Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2007-03

Prothioconazole

The active ingredient prothioconazole and associated end-use product Proline 480 SC Foliar Fungicide, containing the prothioconazole for the control or suppression of Ascomycetes, Basidiomycetes and Deuteromycetes diseases on chickpeas, lentils, canola, rapeseed, Oriental mustard, wheat and barley have been granted temporary registration under the Pest Control Products Regulations.

This Regulatory Note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.pmra-arla.gc.ca
Information Service:
1-800-267-6315 or 613-736-3799
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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of prothioconazole and the associated end-use product Proline 480 SC Foliar Fungicide. This active ingredient and the associated end-use product were reviewed as part of a Joint Review with the United States Environmental Protection Agency (USEPA). The PMRA has concluded that the use of prothioconazole and the end-use product Proline 480 SC Foliar Fungicide in accordance with the label directions has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. Therefore, based on the considerations outlined above, the use of prothioconazole and Proline 480 SC Foliar Fungicide for the control or suppression of Ascomycetes, Basidiomycetes and Deuteromycetes diseases on chickpeas, lentils, canola, rapeseed, Oriental mustard, wheat and barley is proposed for temporary registration pursuant to the Pest Control Products Regulations.

Bayer CropScience will provide additional toxicology, storage stability and livestock feeding data as well as will carry out additional residue chemistry studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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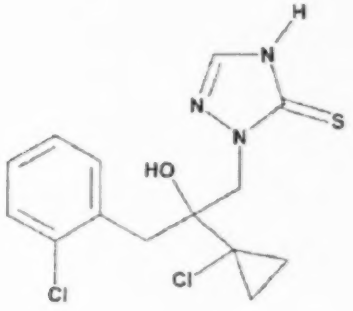
1.0 The Active Substance, Its Properties and Uses

1.1 Identity of the Active Substance and Impurities

Identification of the Technical Grade Active Ingredient

Active substance		Prothioconazole
Function		Fungicide
Chemical name		
1.	International Union of Pure and Applied Chemistry	(*R,S*) 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione.
2.	Chemical Abstracts Service (CAS)	2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione
CAS number		178928-70-6
Molecular formula		$C_{14}H_{15}Cl_2N_3OS$
Molecular weight		344.3
Structural formula		
Nominal purity of active ingredient		97.7% (95.5–100%)
Identity of relevant impurities of toxicological, environmental or other significance		The technical grade prothioconazole does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances.

1.2 Physical and Chemical Properties of the Active Substance and End-Use Product

Technical Product: Prothioconazole

Property	Result	Comment
Colour and physical state	Colourless powder	
Odour	Faint, uncharacteristic odour	
Melting point or range	139.1–144.5°C	
Boiling point or range	Not applicable	
Density at 20°C	1.36 g/mL	
Vapour pressure	**Temperature (°C)** — **Vapour Pressure (Pa)** 20 — $<< 4 \times 10^{-7}$ 25 — $<< 4 \times 10^{-7}$	Low potential for residues on fruits and foliage to decrease as a result of volatilization Not volatile from water
Henry's law constant at 20°C	4.5×10^{-12} atm × m^3/mol	Expected to be non-volatile from water or moist soil
Ultraviolet (UV)–visible spectrum	Peak maxima at 257 nm. No absorption at > 300 nm.	Photodegradable in the UV range
Solubility in water at 20°C (g/L)	**pH** — **Solubility** 4 — 0.005 8 — 0.3 9 — 2.0	Soluble at neutral and acidic pH, but very soluble at alkaline pH
Solubility in organic solvents at 20°C (g/L)	**Solvent** — **Solubility** Acetone — > 250 Acetonitrile — 69 Dichloromethane — 88 Dimethylsulfoxide — 126 Ethylacetate — > 250 1-Octanol — 58 2-Propanol — 87 Xylene — 8	In general, solubility appears to increase with increasing organic solvent polarity

Property	Result		Comment
n-Octanol–water partition coefficient (K_{ow}) at 20°C	**pH** water 4 7 9	**log K_{ow}** 4.05 4.16 3.82 2.0	Potential for bioaccumulation under acid to neutral pH conditions
Dissociation constant (pK_a)	$pK_a = 6.9$		
Stability (temperature, metal)	Thermally stable at room temperature under air. Stable to most metals. Colour changes observed in the presence of copper materials.		

End-Use Product: Proline 480 SC Fungicide

Property	Result
Colour	Off-white
Odour	Slight latex paint odour
Physical state	Liquid
Formulation type	Suspension concentrate
Guarantee	480 g a.i./L nominal (limits: 466–494 g a.i./L)
Formulants	The product does not contain any PMRA List 1 formulants or formulants known to be TSMP Track 1 substances
Container material and description	High density polyethylene bottles.
Bulk density	1.17 g/mL at 20°C
pH	7.0 for a 10% dilution in distilled water.
Oxidizing or reducing action	The product has no oxidizing or reducing properties.
Storage stability	The product was shown to be stable for at least one year under warehouse conditions
Explodability	The product does not have any explosive properties.

1.3 Details of Uses and Further Information

The active ingredient prothioconazole (JAU 6476) and the associated end-use product Proline 480 SC Foliar Fungicide is a new systemic fungicide from Bayer CropScience submitted for joint registration in the United States and Canada. Prothioconazole is a Group 3 Fungicide, specifically within the demethylation inhibitor (DMI) class of sterol biosynthesis inhibitors (sterol biosynthesis inhibitor [SBI] fungicides). Proline 480 SC is formulated as a soluble concentrate, with a guarantee of 480 g prothioconazole per litre of product.

Proline 480 SC is a foliar-applied fungicide for use on several cereal and vegetable crops, including barley, wheat (spring, durum and winter), canola, rapeseed, Oriental mustard, chickpeas and lentils. Proposed application rates range from 210 to 420 mL product/ha (100–200 g a.i./ha), with a maximum of 2 applications or 735 mL/ha per year for wheat and barley, and 3 applications or 840 mL product/ha to be made per year for canola, chickpeas and lentils.

Bayer CropScience proposed that Proline 480 SC will suppress or control the following cereal diseases: fusarium head blight (also known as scab, which is caused by various *Fusarium* species), net blotch (*Pyrenophora teres*), scald (*Rhynchosporium secalis*), spot blotch (*Cochliobolus sativus*), Septoria glume blotch (*Stagonosora nodorum*), Septoria leaf spot (*Septoria tritici*), tan spot (*Pyrenophora tritici-repentis*) and leaf rust (*Puccinia recondita*). Proline 480 SC is also proposed for control of Sclerotinia stem rot (*Sclerotinia sclerotiorum*) on canola, rapeseed and Oriental mustard, and Ascochyta blight (*Ascochyta* spp.) on chickpeas and lentils.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Substance as Manufactured

Prothioconazole and the impurities present in the technical product were determined by high performance liquid chromatography (HPLC) with UV detection. The active ingredient and impurities were quantitated using a diethylphthalate internal standard and an external standard calibration, respectively. The methods were shown to be precise with a relative standard deviation for the active ingredient of 0.31% and a relative standard deviation ranging from 0.24 to 0.40% for the impurities. Specificity was demonstrated by the absence of interferences at the retention times of the analytes of interest.

2.2 Methods for Formulation Analysis

An HPLC method was used for the determination of prothioconazole in the formulation. Quantitation was by internal standard using butyl benzoate. The method was shown to be linear, precise (relative standard deviation of 0.61%) and accurate (mean recovery of 99.4%). Specificity was demonstrated by the absence of interferences at the retention time of the analyte of interest. The method is acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

2.3.1 Methods for Environmental Residue Analysis

2.3.1.1 Analytical Methodology (parent compound and transformation products)—Soil

Residues of the parent compound, prothioconazole and the transformation products, prothioconazole-desthio, prothioconazole-thiazocine and prothioconazole-*S*-methyl were extracted from soil using acetonitrile/water/cysteine hydrochloride, 800:200:0.5, v/v/w. The resulting extract was analyzed by high performance liquid chromatography (with electrospray ionization) and tandem mass spectrometry (LC-MS/MS), and quantitation was done against known amount of heavy isotopic internal standards. The average recoveries of prothioconazole, desthio, *S*-methyl and thiazocine spiked at the 10 ppb level were 98.3, 103.1, 101.4 and 99.7%, respectively. The limit of quantitation (LOQ) of prothioconazole and the metabolites in soil has been established at 10 ppb. The relative standard deviation ranged from 2.9 to 7.0% (n = 12). No analytical interferences were observed at the retention times of the analytes. Based on the chromatograms and validation data, the method is acceptable to be used as postregistration monitoring method.

2.3.1.2 Analytical Methodology (parent compound and transformation products)—Sediment

The analytical methodology for sediment is addressed in Section 2.3.1.1.

2.3.1.3 Analytical Methodology (parent compound and transformation products)—Water

Residues of the parent compound prothioconazole and the transformation products prothioconazole-desthio, prothioconazole-thiazocine and prothioconazole-*S*-methyl were extracted from water with C18 solid phase extraction (SPE) cartridge and eluted with acetonitrile/water (9:1, v/v). The resultant solution was analyzed by LC-MS/MS. The method was validated from control water obtained from New Port, Arkansas, at 0.3 ppb and 3 ppb. The average recoveries of prothioconazole, desthio, *S*-methyl and thiazocine spiked at the 0.3 ppb level were 96, 107, 103 and 104%, respectively. The average recoveries of prothioconazole, desthio, S-methyl and thiazocine spiked at the 3 ppb level were 99% for all four analytes. The LOQ of prothioconazole and its transformation products in water has been established at 10 ppb.

A LC-MS/MS was used for the determination of 1,2,4-triazole in water from Live Oak, California. Isotopic internal standard of triazole was added to the water sample. The extract was derivatized with dansyl chloride to form a dansyl triazole derivative. The derivative was partitioned with ethyl acetate and dried with anhydrous sodium sulfate. It was then concentrated to dryness and reconstituted with acetonitrile. The concentrated extract was analyzed by LC-MS/MS operated in positive ionization mode. The average recoveries of triazole from all water spiked at 0.10 ppb ranged from 109% to 114%, and at 1.00 ppb the range was from 100% to 102%. The LOQ for 1,2,4-triazole has been established at 0.1 ppb.

Based on the chromatograms and validation data, the methods for the determination of the residues of the parent compound and its transformation products in water are acceptable to be used as postregistration monitoring methods.

2.3.2 Multiresidue Methods for Residue Analysis

Prothioconazole, prothioconazole-desthio, prothioconazole-4-hydroxy, triazole and triazolylacetic acid were tested through the United States Food and Drug Administration multiresidue method test guidelines in the *Pesticide Analytical Manual*, Volume I (1994). The results demonstrated that prothioconazole-derived residues were not adequately recovered in plant or animal matrices under the various multiresidue method protocols tested. Given the test results, the multiresidue methods are not appropriate for determining the prothioconazole residue definition or for determining residues of triazole, triazolylalanine or triazolylacetic acid.

2.3.3 Methods for Residue Analysis of Plants and Plant Products

A LC-MS/MS method was developed and proposed for data gathering and enforcement purposes. In plant matrices, an oxidative extraction procedure converted prothioconazole residues to a mixture of prothioconazole-desthio and prothioconazole sulfonic acid. The results were reported as prothioconazole equivalents. The method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method LOQ. Acceptable recoveries (70–120%) were obtained and adequately bracketed the expected residue levels in representative plant matrices. Adequate extraction efficiencies were achieved using radiolabelled residues from wheat forage and sugarbeet tops analyzed with the enforcement method. Confirmatory analysis procedures were not necessary due to the high specificity of the LC-MS/MS method.

2.3.4 Methods for Residue Analysis of Food of Animal Origin

A LC-MS/MS method was developed for data gathering and enforcement of maximum residue limits in milk and cattle tissues. In animal matrices, extracts were hydrolyzed with acid and residues were reported as prothioconazole equivalents (prothioconazole, prothioconazole-desthio, prothioconazole-4-hydroxy, including conjugates that may be converted to these compounds by acid hydrolysis). The method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method LOQ. Acceptable recoveries (70 to 120%) were obtained in representative animal matrices. Adequate extraction efficiencies was demonstrated using radiolabelled residues from goat milk, goat liver, goat muscle and goat fat analyzed with the enforcement method. Confirmatory analysis procedures were not conducted for the proposed enforcement method due to the high specificity of the proposed LC-MS/MS method.

3.0 Impact on Human and Animal Health

3.1 Integrated Toxicological Summary

A detailed review of the toxicological databases for prothioconazole (also referred to in this document as "parent") and its major metabolite prothioconazole-desthio (referred to as "desthio") were conducted. The databases are complete, consisting of the full array of toxicity studies currently required for regulatory purposes. The studies were carried out in accordance with currently accepted international testing protocols and good laboratory practice (GLP). The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical.

Prothioconazole (98.8–99.8%) was considered to be of low acute toxicity by the oral, dermal and inhalation routes in Wistar rats. It was non-irritating when applied to the eyes or skin of Himalayan rabbits. The results of skin sensitization testing in guinea pigs, using the maximization method, were negative.

The following prothioconazole plant metabolites and impurities were tested in Wistar rats and fell into the low-toxicity category:

- prothioconazole-asymmetric isomer;
- prothioconazole-methyl;
- prothioconazole-asymmetric disulfide;
- prothioconazole-alpha hydroxy desthio;
- prothioconazole-alpha acetoxy desthio;
- prothioconazole-benzylpropyldiol;
- prothioconazole-triazolinone; and
- prothioconazole-deschloro.

Additionally, prothioconazole-sulfonic acid potassium salt is considered highly acutely toxic. Prothioconazole-deschloro was found to be a dermal sensitizer in guinea pigs using the maximization method.

Desthio (93.7–95.4%) was considered to be of low acute toxicity by the oral route in Wistar rats and NMRI mice. Although mortality was low at high doses, there were several clinical observations such as decreased motility, apathy, laboured breathing and spasmodic states. An intraperitoneal injection gave a lethal dose 50% (LD_{50}) in the 450 to 630 mg/kg range. Desthio was also considered to be of low acute toxicity by the dermal and inhalation routes in Wistar rats. Desthio was slightly irritating to the eyes and non-irritating to the skin of New Zealand white rabbits. It was not considered to be a sensitizer in guinea pigs using the Buehler method.

Proline 480 SC Foliar Fungicide was of low acute toxicity by the oral and dermal routes in Wistar rats and slightly acutely toxic by the inhalation route in the same species; there was no mortality, but the testing concentration was not high enough to verify a low toxicity status. It was non-irritating when applied to the eyes of New Zealand white rabbits and mildly irritating when applied to the skin of the same species. Results of skin sensitization testing in guinea pigs, using the maximization method, were negative.

Absorption and excretion of single or repeated oral doses of prothioconazole was rapid. A minimum of 90% of the administered dose was absorbed, and excretion was almost complete, with feces (by means of the bile) as the principle route of clearance. Within 48 hours, 86–94% of the administered dose was detected in the urine and feces. Tissue residues declined rapidly, with the highest levels (relative to organ weight, not the administered dose) occurring in the liver, kidney, brown/perirenal fat, thyroid and adrenal gland. Although residual radioactivity was low, it was still about three times higher in females than in males. Apart from that finding, there was little quantitative difference between the sexes for single low/high dosing or repeat dosing.

Eighteen metabolites plus the parent were found in excreta of animals dosed with the parent. The metabolic reaction types were desulfuration, oxidative hydroxylation of the phenyl moiety and glucuronic acid conjugation. In the feces, the parent was the most common, followed by desthio. All other metabolites were less than 8% of the administered dose. For urine, the major metabolites were prothioconazole-*S*- or -*O*-glucuronide. No significant differences were observed between sexes.

The toxicokinetic profile of desthio is similar to the parent. Ninety percent of administered dose was excreted in bile and urine at 48 hours. Five to six percent remained in the carcass at that point. Desthio preferentially accumulated in fat over plasma; however, the total fraction of administered dose was very small. In a pregnant rat toxicokinetic study, rats dosed with 1 or 3 mg/kg orally or 30 mg/kg dermally displayed similar plasma concentrations after single or multiple dosing. The dermal high dose (100 mg/kg) provided a 3-fold higher plasma concentration after repeat versus single dosing. Repeat doses to the skin were poorly absorbed (approximately 5–10% achieved systemic circulation).

A short-term (28-day) dermal study showed no effects up to the limit dose of 1000 mg/kg bw/day after repeated applications of prothioconazole to the shaved skin of albino rats. No equivalent study was performed with desthio. In a short-term (28-day) inhalation study using Wistar rats and desthio, no treatment-related effects were observed, though the highest dose tested was only a quarter of the limit dose for this study type.

In subchronic and chronic toxicity studies, prothioconazole and desthio targeted the following organs: liver, kidney (parent only), ovaries and thyroid. Desthio consistently produced toxicity at lower dose levels than the parent. Generalized toxicity was observed in rats, mice and dogs as decreases in body weight, body-weight gain, food consumption and/or food efficiency. Water consumption and urine volume were increased in the prothioconazole treated group. Liver toxicity was evident in most studies and included increased size and weight, altered enzyme levels, fatty changes, discolourations as well as occasional hepatocyte hypertrophy and necrosis. Kidney weights increased, and there were increased incidences of crystals/mineralization,

chronic inflammation, pigmentation, basophilic tubules and tubule dilation or degeneration as well as multifocal chronic interstitial fibrosis in the prothioconazole group. Thyroid toxicity was less common, but included increased weights, altered hormone levels (especially decreases in thyroxine [T4]), follicular hypertrophy and colloidal mineralization. Ovary related effects included enlarged appearance, increased weights, increased incidence of stromal edema, hemorrhagic degeneration of the corpora lutea, altered number of corpora lutea and increased tertiary/antral follicles.

Long-term studies in rats and mice provided no evidence of treatment-induced oncogenicity. A cancer potency factor is not necessary for prothioconazole or for desthio.

No evidence of mutagenic potential of technical product prothioconazole was observed in vitro with the Ames bacterial mutation test. Under the conditions of an in vitro mammalian chromosomal aberration assay (cultures of Chinese hamster lung V79 cells), prothioconazole was considered non-clastogenic in one study, but positive in another study (the positive result was considered secondary to cytotoxicity). For unscheduled DNA synthesis, prothioconazole was equivocal in vitro, but negative in vivo (both performed with primary rat hepatocytes). In an in vivo study, prothioconazole did not induce micronuclei in a mouse micronucleus assay. Based on the data presented, prothioconazole was not considered to be genotoxic under the conditions of the tests performed.

The desthio metabolite was negative in all genotoxicity tests, an Ames bacterial mutation test, a gene mutation assay in vitro (V79 cells), a chromosomal aberration assay (V79 cells), unscheduled DNA synthesis in vitro (primary rat hepatocytes) and a micronucleus assay in vivo (NMRI mice).

Several other prothioconazole plant metabolites and impurities (-deschloro, -alpha acetoxy desthio, -sulfonic acid potassium salt, -benzylpropyldiol, -methyl, -asymmetric isomer, -asymmetric disulfide, -alpha hydroxy desthio and -triazolinone) were tested with the Ames bacterial mutation test. All results were negative.

There were signs of teratogenicity at maternally toxic doses in the developmental toxicity studies of rats for prothioconazole (microphthalmia) and at maternally non-toxic doses in the rabbit developmental toxicity study with desthio (arthrogryposis). There was evidence of quantitative sensitivity of the young with desthio, evidenced by supernumerary ribs occurring at maternally non-toxic doses. One extra pair of ribs is generally not considered adverse; however, these extra ribs occurred in multiple pairs (one to three extra pairs) and were not completely reversible as the rats matured. At maternally toxic doses, there were increased incidences of delayed or unossified digits, toes, sternebrae and pubic bones, dysplastic pubic bones, cryptorchidism, angled mouth, dilatation of the renal pelvis, cleft palate, hydrocephaly, hydronephrosis, macroglossia and tubular bone dysplasia. Pup body weights decreased, while postimplantation loss and resorptions increased. Maternal toxicity was similar to that observed in the subchronic studies, with the addition of the following observations: decreased live fetuses per dam, increased placental weights, increased total litter loss and decreased gestation rate.

Two other metabolites and impurities were tested for developmental toxicity in rats. Prothioconazole-deschloro yielded a decreased number of live fetuses, decreased body-weight gains, increased urination and water consumption, slight dilations of the renal pelvis and ureter, increased supernumerary ribs, wavy ribs, retarded ossification of the skull bones as well as macroglossia. The other metabolite, prothioconazole sulfonic acid potassium salt, produced increased mortality in the dams, decreased body-weight gain and food consumption, dams with total litter losses and decreased fetal body weights.

In the reproduction study, generalized toxicity similar to the subchronic studies was observed in parental animals at the highest dose tested. Additionally, with prothioconazole, seminal vesicle weights increased, thymus weights decreased in females, and multifocal cortical nephrosis was seen in males. Females had a decreased number of estrous cycles with an increase in cycle length. Second generation female adults had an increased number of pre-antral follicles. Mated pairs showed an increased time to insemination. The desthio metabolite produced dystocia in several dams, which led to several deaths and sacrifices. Pups in both generations had decreased weight gain during lactation. Offspring toxicity occurred at doses causing parental toxicity. There was an increase in days to preputial separation that was potentially due to the decreased body weights. Viability decreased and several pups were classified as cannibalized or missing. There were increased incidences of enlarged liver, cleft palate, red kidney zones, dilated renal pelvis, dilated ureters and distended bladder. Several pups were described as weak and unthrifty. There was no evidence of quantitative sensitivity.

In an acute neurotoxicity study, treatment with prothioconazole resulted in decreased motor and locomotor activity. A subchronic neurotoxicity study with prothioconazole yielded decreased body weight and body-weight gains. A developmental neurotoxicity study with desthio was found to be deficient (brain morphometrics and the peripheral nervous system were not assessed at low and mid doses, amongst other issues), but several observations were still considered valid: a slight increase in stillborn pups, dystocia, increased gestation time, a slight decrease in mean pups per litter, progressive malocclusion and deviated snouts in pups, increased lesions of the peripheral nerves and increased corpus callosum size in males. Given the lack of brain measurements and examination of peripheral nerves at low and mid doses, it is impossible to rule out an effect at these levels. This uncertainty was incorporated into the reference doses.

Special studies were generated to address several issues. A liver foci test with initiation and regeneration was performed with desthio. The results were consistent with the lack of liver tumours, but also supported the observed liver toxicity. With prothioconazole, an in vitro liver cytochrome study was submitted, but was found to be unacceptable due to multiple deficiencies. An in vitro thyroid peroxidase catalyzed reaction study with hog thyroid microsomes indicated that prothioconazole temporarily suppressed thyroid peroxidate (TPO)-catalyzed iodine formation. This was a qualitative study only. An immunotoxicity study in mice did not show evidence of immunosuppression. The enzyme activities as well as the concentration of prothioconazole in the liver and kidneys were measured in dogs. Epoxide hydrolase increased in the liver of females, but decreased in the kidneys of males. Both of these observations were found to be reversible after four weeks of recovery. Prothioconazole was about 10 times more concentrated in the liver than desthio. There was no desthio detected in the kidneys. Overall tissue concentrations were about three-fold higher in females.

3.2 Toxicological Endpoint for Assessment of Risk Following Long-Term Dietary Exposure—Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for the general population for prothioconazole is 0.004 mg/kg bw/day. The desthio chronic toxicity and oncogenicity study in the rat was considered the most appropriate study to assess chronic dietary exposure. The no observed adverse effect level (NOAEL) was 1.1 mg/kg bw/day, based on liver toxicity. The standard uncertainty factor of 100-fold was applied to account for intraspecies and interspecies variability, and an additional three-fold safety factor was recommended to protect for sensitivity of the young in the desthio developmental neurotoxicity study (malocclusion and deviated snout). This provides margins of safety (MOS) of 900 to the NOAEL for progressive malocclusion and deviated snout in the desthio developmental neurotoxicity study and for the lack of morphometric measurements at the lowest dose tested in the developmental neurotoxicity study.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{1.1 \text{ mg/kg bw/day}}{300} = 0.004 \text{ mg/kg bw/day}$$

The recommended ADI for females 13+ for prothioconazole is 0.002 mg/kg bw/day. The desthio rabbit developmental study was considered the most appropriate study to assess chronic dietary exposure. The NOAEL was 2 mg/kg bw/day, based on fetal malformations (arthrogryposis). The standard uncertainty factor of 100-fold was applied to account for intraspecies and interspecies variability, an additional 10-fold safety factor was recommended to protect for severity of endpoint in the fetus as the malformations occurred at maternally non-toxic doses. This provides margins of safety of 1800 to the NOAEL for progressive malocclusion and deviated snout and for the lack of morphometric measurements at the lowest dose tested in the developmental neurotoxicity study. There is a MOS of 40 000 to the lowest observed adverse effect level (LOAEL) for microphthalmia in the prothioconazole rabbit developmental study.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{2 \text{ mg/kg bw/day}}{1000} = 0.002 \text{ mg/kg bw/day}$$

3.3 Toxicological Endpoint for Assessment of Risk Following Acute Dietary Exposure—Acute Reference Dose

There are no acute effects of concern for the general population. The only potential concern is the uncertainty around the developmental neurotoxicity study regarding altered brain morphometrics and peripheral nerve degeneration due to a lack of measurements at low and mid doses. Consequently, it is appropriate to set a reference dose for females 13+. The prothioconazole-desthio rabbit developmental study was considered the most appropriate study to assess acute dietary exposure. The NOAEL was 2 mg/kg bw/day, based on fetal malformations (arthrogryposis). The standard uncertainty factor of 100-fold was applied to account for intraspecies and interspecies variability, and an additional 10-fold safety factor was

recommended to protect for severity of endpoint in the fetus as the malformations occurred at maternally non-toxic doses. The recommended acute reference dose (ARfD) for females 13+ is 0.002 mg/kg bw.

$$\text{ARfD (females 13+)} = \frac{\text{NOAEL}}{\text{UF}} = \frac{2 \text{ mg/kg bw}}{1000} = 0.002 \text{ mg/kg bw}$$

3.4 Toxicological Endpoint for Assessment of Occupational and Bystander Risks

Occupational exposure is characterized as short-term or intermediate-term and is predominately by the dermal route. A dermal developmental study with desthio and a 28-day dermal toxicity study with prothioconazole were available. The desthio study with a developmental NOAEL of 30 mg/kg bw/day based on increased incidences of supernumerary ribs at 100 mg/kg bw/day was considered appropriate for use as a toxicological endpoint. A margin of exposure (MOE) of 300 is recommended based on 100-fold to account for intraspecies and interspecies difference and an additional 3-fold to account for severity of effects in the young (variations at maternally non-toxic doses). This endpoint will also be considered appropriate for assessing long-term dermal exposures.

For short-term and intermediate-term inhalation and oral exposures, the desthio rabbit developmental NOAEL of 2 mg/kg bw/day with an MOE of 1000 is the most appropriate (100-fold to account for intraspecies and interspecies difference and an additional 10-fold to account for severity of endpoint with malformations at maternally non-toxic doses).

The dermal and inhalation assessments are not to be combined. The two studies used for individual assessments do not share a common endpoint with the rat dermal developmental study having supernumerary ribs, whereas the rabbit developmental study has the malformation arthrogryposis.

3.5 Impact on Human and Animal Health Arising From Exposure to the Active Substance or to Its Impurities

3.5.1 Operator Exposure Assessment

3.5.1.1 Handler Exposure and Risk

The applicant submitted an operator exposure study carried out in Monheim, Germany, to measure the exposure of operators to prothioconazole and its degradation product prothioconazole-desthio when applying the product by groundboom to cereals. The purpose of the study was to determine the dermal and inhalation exposure to prothioconazole during application as well as to determine the proportion of conversion of prothioconazole to prothioconazole-desthio and the resulting exposure to prothioconazole-desthio.

This study was reviewed and is not considered adequate to estimate exposure of mixer/loader/applicators due to study limitations. This study did, however, demonstrate that both prothioconazole and the desthio metabolite are present during occupational use of prothioconazole formulations. The desthio metabolite was found in the tank mixture in this study; therefore, it is present from the beginning of worker exposure scenarios.

The Pesticide Handlers Exposure Database (PHED) was used to estimate exposure of workers mixing, loading and applying Proline 480 SC Foliar Fungicide. Handlers mixing, loading and applying Proline 480 SC Foliar Fungicide are expected to be exposed to a mixture of prothioconazole and prothioconazole-desthio for a short- to intermediate-term duration. Exposure estimates for mixers, loaders, applicators are based on data from the PHED. The PHED version 1.1 is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. With a few exceptions, the PHED estimates meet criteria for data quality, specificity and quantity outlined by the North American Free Trade Agreement Technical Working Group on Pesticides. To estimate exposure for each use scenario, appropriate subsets of A and B data were created for liquid mixer/loader and aerial and groundboom (open cab) applicator from the PHED. All data were normalized for kilogram of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, such as mean, median or geometric mean, i.e., summing the measure of central tendency for each body part.

Exposure estimates to workers mixing/loading and applying Proline 480 SC Foliar Fungicide are summarized in Table 3.5.1. For all scenarios, it was assumed that workers would wear the personal protective equipment specified on the proposed label (i.e., long pants, a long-sleeved shirt and gloves during mixing and loading, and long pants and a long-sleeved shirt during application).

Table 3.5.1 Exposure Estimates for Workers Handling Proline 480 SC Foliar Fungicide

Scenario	Dermal Exposure[1] (µg/kg bw/day)	Inhalation Exposure[1] (µg/kg bw/day)
Farmer Groundboom	36.05	1.1
Custom Groundboom	72.1	2.19
Aerial Mixer/Loader	62.65	1.6
Aerial Applicator	11.83	0.07

[1] Exposure = amount of active ingredient handled (kg a.i. handled/day) × PHED unit exposure (µg/ kg a.i. handled) × absorption (100% for both dermal and inhalation) / body weight (70 kg). Amount of active handled per day is based on the application rate (0.2 kg a.i./ha for groundboom, 0.175 kg a.i./ha for aerial) × area treated per day (150 ha for farmer using groundboom equipment, 300 ha for custom applicators using groundboom equipment, 490 ha for aerial applicators)

Four in vivo dermal absorption studies were submitted in support of this submission: two for prothioconazole (one rodent, one primate) and two for prothioconazole-desthio (both primate). These studies were reviewed and demonstrate significant potential for dermal absorption; however, a dermal absorption value was not required for the risk assessment because a dermal toxicology endpoint was used.

Table 3.5.2 Risk Estimates for Workers Handling Proline 480 SC Foliar Fungicide

Scenario	Dermal MOE[1]	Inhalation MOE[2]
Farmer Groundboom	832	1823
Custom Groundboom	416	911
Aerial Mixer/Loader	479	1020
Aerial Applicator	2535	23324

1 Based on a NOAEL of 30 mg/kg bw/day from a rat dermal developmental study; target MOE = 300
2 Based on a NOAEL of 2 mg/kg bw/day based on an oral rabbit developmental study; target MOE = 1000

All dermal MOEs for workers mixing, loading and applying Proline 480 SC Foliar Fungicide at the maximum application rate of 200 g a.i./ha by groundboom or 175 g a.i./ha by aerial application scenarios are above the target MOE of 300 when the proposed personal protective equipment is worn (Table 3.5.2). The MOEs for inhalation exposure are above the target for farmers applying Proline 480 SC Foliar Fungicide with groundboom equipment and for aerial mixer/loaders and applicators, but are slightly below the target of 1000 for custom application using groundboom equipment. However, this MOE is considered acceptable for the following reasons.

- Workers are expected to be exposed to a combination of prothioconazole and prothioconazole-desthio; however, the toxicological endpoint for the inhalation NOAEL is based on the desthio metabolite, which appeared to be more toxic than the parent compound.

- The risk assessment for custom applicators is based on one worker mixing, loading and applying Proline 480 SC Foliar Fungicide to treat 300 ha with open-cab groundboom equipment. This is a high-end estimate as custom applicators may not always treat 300 ha in a day and closed-cab equipment is often used when treating large areas.

3.5.1.2 Re-entry Worker Exposure and Risk

There is potential for workers re-entering fields treated with Proline 480 SC Foliar Fungicide to be exposed to foliar residues of prothioconazole and prothioconazole-desthio. The product may be applied up to 3 times on chickpeas and lentils, at an application interval of 10–14 days over the season. The exposure duration for the other proposed crops is expected to be shorter because fewer applications have been proposed and/or the application interval is shorter. As such, exposure is expected to be of short- to intermediate-term duration.

Workers are expected to be exposed to foliar residues of prothioconazole and prothioconazole-desthio primarily by the dermal route when reentering treated fields to perform activities such as scouting, irrigation and weeding. A transfer coefficient of 1500 cm^2/hour is considered appropriate for scouting and irrigation and a transfer coefficient of 100 cm^2/hour is considered appropriate for hand and mechanical weeding in all of the proposed crops. The inhalation route is not expected to contribute significantly to re-entry exposure.

No data on dislodgeable foliar residues were submitted in support of this submission; therefore, a default initial dislodgeable foliar residue level of 20% of the application rate with a dissipation rate of 10% per day was used to estimate the exposure of re-entry workers. Estimations of dislodgeable foliar residues and worker exposure and risk are summarized in Table 3.5.3.

Table 3.5.3 Exposure and Risk Estimates for Workers Reentering Fields Treated With Proline 480 SC Foliar Fungicide

Crop	Dislodgeable Foliar Residue on Final Day Application ($\mu g/cm^2$)	Exposure[1] (μg/kg bw/day)	MOE[2]	Required REI (days)
Chickpeas, lentils	0.588	100.8	298	1
Canola, rapeseed, Oriental mustard	0.35	60	500	0
Cereals (wheat and barley)	0.591	101.4	296	1

1 Exposure = dislodgeable foliar residue ($\mu g/cm^2$) × transfer coefficient (cm^2/hour) × exposure duration (8 hours) / body weight (70 kg)

2 Based on a NOAEL of 30 mg/kg bw/day from a rat dermal developmental study; target MOE = 300

MOEs were found to be acceptable for all proposed crops on the day following the final application; therefore, the proposed re-entry interval of 24 hours is acceptable for these crops.

4.0 Residues Summary

The metabolism of prothioconazole was investigated in plants following foliar spray applications of [triazole-UL-^{14}C] or [phenyl-UL-^{14}C]-prothioconazole to wheat, peanuts and sugar beets as well as seed treatment application of [phenyl-UL-^{14}C]-prothioconazole to wheat. With the exception of the label-specific metabolites, the metabolic profiles were very similar for the target crop studies with both radiolabel studies. Irrespective of the mode of application (foliar or seed treatment) and the target crop (wheat, peanuts or sugar beets), the major residues found in all crops were prothioconazole-desthio, triazolylalanine, triazolylacetic acid and triazolylhydroxypropionic acid. The metabolic profiles for the target crop were also similar to the profiles found in the rotational crops. The metabolic pathway for prothioconazole was evaluated in livestock following three consecutive daily oral doses of [phenyl-UL-^{14}C] or

[triazole-UL-^{14}C]-prothioconazole to lactating goats and laying hens. Some qualitative and quantitative differences between goats and laying hens were observed, but were not considered to impact the overall metabolic profile assessment. Conjugation of the unchanged parent compound with glucuronic acid forming an *S*-glucuronide, and desulfuration of prothioconazole yielding prothioconazole-desthio were major metabolic processes in poultry and goats. The majority of the metabolites found in poultry and goats were products of hydroxylation of prothioconazole and the desthio metabolite leading to the formation of the corresponding dihydroxy and dihydroxy-dienes.

Crop field trial data reflected the proposed use pattern for Proline® 480 SC Fungicide formulation on wheat, barley, canola, rapeseed, Oriental mustard, chickpeas and lentils. Processing data indicated that total prothioconazole-derived residues concentrated 7.9-fold in peanut meal, 4.4-fold in rice hulls, 2.4-fold in wheat bran and 2.0-fold in wheat germ. However, expected total prothioconazole-derived residues in the processed fractions will be covered by the respective agricultural commodities maximum residue limits (MRLs). The submitted field rotational crop data, which indicated no quantifiable total prothioconazole-derived residues in mustard greens, turnip root and top, and wheat forage, hay, grain and straw at the one-month plantback interval, are adequate to support the proposed rotational crop restrictions. The available storage stability data are tentatively adequate to support the storage intervals and conditions of samples from all associated field trials.

Confirmatory storage stability data are required in plant commodities to support the length of freezer storage in all studies. Adequate cattle feeding studies with prothioconazole and prothioconazole-desthio have been submitted, which indicate that maximum residue limits for livestock commodities are required. A poultry feeding study and method validation of poultry matrices are required as confirmatory data based on the results of the hen metabolism study because residues are anticipated in poultry liver. The available storage stability data for animal commodities are adequate to support the proposed uses. However, supporting storage stability data for cattle fat samples are required to confirm that residues of prothioconazole, prothioconazole-desthio and prothioconazole-4-hydroxy are stable during freezer storage.

The proposed domestic use of prothioconazole on various commodities (wheat, barley, canola, rapeseed, oriental mustard, chickpea and lentils) does not pose an unacceptable chronic or acute dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and Behaviour in the Environment

The residues relevant to the environment are the active ingredient prothioconazole and the following major transformation products (> 10% of applied radioactivity): prothioconazole-desthio, prothioconazole-*S*-methyl, prothioconazole-thiazocine and 1,2,4-triazole. Prothioconazole-desthio is a major transformation product formed during phototransformation on soil and in water as well as in aerobic soil and aquatic aerobic systems. Prothioconazole-*S*-methyl is a major transformation product in aerobic soil systems as well as in aerobic and anaerobic aquatic systems. Both of these transformation products are expected to form in large quantities in terrestrial and aquatic environment compartments. In addition, based on submitted

toxicity studies, prothioconazole-desthio and prothioconazole-*S*-methyl exhibit similar toxicity to prothioconazole. Therefore, because these transformation products are expected to form at high concentrations and are transformation products of concern, both are considered along with prothioconazole in this assessment, as part of a total toxic residue approach.

Prothioconazole-thiazocine is a major transformation product formed during aquatic phototransformation only, at less than 15% of the parent. It is unlikely to be found in significant concentrations in the environment. There is low concern associated with this transformation product; therefore, it will not be considered in this assessment. 1,2,4-Triazole is a major transformation product formed during aquatic phototransformation and in aerobic aquatic systems. It is also a major transformation product in terrestrial field dissipation studies. Little fate and behaviour as well as toxicity data were submitted for this transformation product, but information was available from a published review of hexaconazole, another active ingredient, because 1,2,4-triazole is a transformation product common to many active ingredients.

5.1 Physical and Chemical Properties Relevant to the Environment

Prothioconazole has low solubility at an acidic pH 4 and very high solubility at a basic pH . The high solubility of prothioconazole at environmental pH is an indicator of a potential for leaching. The vapour pressure indicates prothioconazole is non-volatile, and the Henry's law constant indicates it is not expected to volatilize from water or moist soil surfaces (USEPA 1975). The log K_{ow} indicates a potential for bioaccumulation at pH $\leq$ 7. The maximum UV absorption at a wavelength (λ) of 275 nm and the absence of absorption expected at $\lambda > 300$ nm indicate a low potential for phototransformation under environmentally relevant conditions.

Prothioconazole-desthio is soluble in water and, based on its log K_{ow} , has the potential for bioaccumulation in biological tissue. UV–absorption data indicate a low potential for phototransformation under environmentally relevant conditions. Prothioconazole-*S*-methyl has the potential to bioaccumulation in biological tissue, based on its log K_{ow} . No other physical-chemical properties were available for prothioconazole-*S*-methyl. Physical-chemical properties of 1,2,4-triazole and prothioconazole-thiazocine relevant to the environment were not available.

Summaries of the available physical-chemical properties and molecular structures of prothioconazole as well as the major transformation products prothioconazole-desthio, prothioconazole-*S*-methyl, prothioconazole-thiazocine and 1,2,4-triazole are provided in Appendix III, Tables 1 to 5.

5.2 Abiotic Transformation

Hydrolysis is not expected to be an important route of transformation for prothioconazole or the transformation product prothioconazole-desthio, as both compounds are stable to hydrolysis at environmentally relevant pHs.

Phototransformation on soil surfaces is not an important route of transformation in the environment for prothioconazole or prothioconazole-desthio. Transformation was slower in the irradiated soil than in the dark control samples; therefore, all transformation was attributed to biotransformation. Prothioconazole and prothioconazole-desthio are considered stable to phototransformation on soil. No data were available for prothioconazole-*S*-methyl.

The aqueous phototransformation half-life of prothioconazole and prothioconazole-desthio together was 19.9 days of continuous irradiation (equivalent to 101.9 days in New York, New York, in June sunlight). This is mainly the result of prothioconazole transforming to prothioconazole-desthio, which then persists under further irradiation. Other major transformation products of aqueous phototransformation are prothioconazole-thiazocine and 1,2,4-triazole. Phototransformation is not expected to be a major route of prothioconazole and prothioconazole-desthio transformation in water given that the predicted environmental half-life is greater than seven days. No data were available for prothioconazole-*S*-methyl.

Based on the vapour pressure and Henry's law constant for prothioconazole, volatility is not expected to be a major route of dissipation for prothioconazole. No information on vapour pressure or Henry's law constant was available for prothioconazole-desthio and prothioconazole-*S*-methyl.

In general, abiotic transformation of prothioconazole and prothioconazole-desthio is expected to be minimal under environmental conditions. Abiotic transformation is summarized in Appendix III, Tables 6 to 9.

5.3 Biotransformation

Biotransformation of total toxic residues is summarized in Appendix III, Tables 6 to 9.

Two aerobic biotransformation studies in soil conducted on four soils were submitted and useable for quantitative estimates of aerobic biotransformation of prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl together. The three chemicals have similar toxicity; therefore, these three components were combined in estimates of aerobic soil biotransformation. Half-lives of prothioconazole and transformation products alone may substantially underestimate actual persistence.

Prothioconazole dissipates rapidly in aerobic soils (only 7.9–52.1% of applied radioactivity one day after application and < 2.0–23.2% of applied radioactivity after 7 days) by transforming to prothioconazole-desthio and prothioconazole-*S*-methyl, which are more persistent in soil. Incorporation to non-extractable soil residues is also an important component of the fate of total toxic residues of prothioconazole in soil (2.7–10.9% of applied radioactivity at time zero and 20.6–52.7% of the applied radioactivity from day 1 until study termination in all soils). Prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl were partly mineralized to carbon dioxide (0.7–17.9% of the applied radioactivity).

The dissipation of total toxic residues (prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl) in aerobic soil was characterized by a rapid initial phase followed by a second, slower dissipation phase. The total toxic residues are non-persistent to moderately persistent in aerobic soil (dissipation time 50% [DT_{50}] 3.6–95.2 days), according to the scheme of Goring et al. (1975).

Aerobic aquatic biotransformation of prothioconazole was studied in pond water-loam sediment and in lake water-loamy sand sediment systems. Prothioconazole rapidly transformed in addition to partitioning from the water column to the sediment. A large proportion of the radioactivity in the sediment was associated with the non-extractable phase, especially in the pond water-loam sediment system (45.3–46.7% of applied radioactivity at the end of the 121-day study period). Major transformation products in aerobic aquatic systems were prothioconazole-desthio, prothioconazole-*S*-methyl and 1,2,4-triazole. The dissipation of total toxic residues from aerobic water systems was characterized by an initial rapid decline followed by a slower dissipation phase. Total toxic residues are classified as slightly persistent in aerobic aquatic systems (total system DT_{50}s 28.6–41.5 days), according to the classification scheme of McEwen and Stephenson (1979). 1,2,4-Triazole is expected to be persistent and accumulate in aerobic aquatic systems, reaching maximum concentrations at the end of the 121-day study period.

In anaerobic aquatic systems, prothioconazole partitioned from the water column to the sediment. Contrary to aerobic aquatic biotransformation, the only major transformation product was prothioconazole-*S*-methyl (maximum of 78.2% in the total system), which persists in anaerobic aquatic environments. The dissipation of total toxic residues was very slow, with a half-life of 1386.3 days, indicating that total toxic residues are persistent under anaerobic aquatic conditions, according to the classification scheme of McEwen and Stephenson (1979). The proportion of the radioactivity in the sediment associated with the non-extractable phase was smaller than in aerobic aquatic systems (26.4% at the end of the 360-day study period).

5.4 Mobility

Prothioconazole is not expected to volatilize from dry or moist surfaces under field conditions given its vapour pressure and the Henry's law constant. Mobility in soil was classified according to the classification scheme of McCall et al. (1981). Batch equilibrium studies could not be conducted with prothioconazole due to instability of the chemical in the system. Based on results of column leaching studies, prothioconazole has very low potential to leach; it did not migrate from the top treated soil layer of 0–6 cm in unaged leaching study, and only 1.01 and 0.36% of the applied radioactivity were attributed to prothioconazole in the 0–6 and 6–12 cm soil layers in the aged leaching study. Prothioconazole has slight to low mobility in soils based on the results of an HPLC study and modelling of physical-chemical properties.

Soil column leaching studies indicate transformation products are expected to be slightly more mobile than prothioconazole in soil. Based on batch equilibrium adsorption studies, prothioconazole-desthio is expected to have low to moderate mobility in soil, prothioconazole-*S*-methyl has slight mobility in soil, and 1,2,4-triazole is expected to have moderate to high mobility in soils. Prothioconazole-thiazocine is expected to have high mobility in soil based on results of an HPLC study.

The leaching potential for prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl was estimated with the groundwater ubiquity score (GUS) (Gustafson 1989) and using combined half-lives for the three compounds in aerobic soil. Prothioconazole and prothioconazole-*S*-methyl are classified as non-leachers while prothioconazole-desthio is expected to be a non-leacher to a borderline leacher.

The mobility of total toxic residues and other major transformation products of prothioconazole is summarized in Appendix III, Table 6.

5.5 Dissipation and Accumulation Under Field Conditions

The dissipation and accumulation of total toxic residues under terrestrial field conditions are summarized in Appendix III, Tables 6 and 7.

Based on the results of field dissipation trials, total toxic residues (prothioconazole and transformation products prothioconazole-desthio and prothioconazole-*S*-methyl) are not expected to leach to groundwater in significant quantities, but there is the potential for toxic transformation products to carry over to the following growing season. Major transformation products were prothioconazole-desthio and 1,2,4-triazole, while prothioconazole-*S*-methyl was a minor transformation product under field conditions. Prothioconazole-thiazocine was not detected in any sampling interval, at any depth, at any site.

The dissipation of total toxic residues followed first-order kinetics in a New York field site, while it was biphasic in the Canadian field sites. One application of the prothioconazole formulation JAU6476 480 SC to bare field test plots at 221 g a.i./ha (110% of the Canadian maximum rate for a single application of 201 g a.i./ha) in Manitoba and Saskatchewan resulted in non-first-order DT_{50}s and dissipation times 90% (DT_{90}s) for total toxic residues of 8.2 days and 756 days, respectively, in Manitoba, and 111.6 days and 1117 days, respectively, in Saskatchewan. In New York, prothioconazole formulation applied 6 times, each at 336 g a.i./ha (167% of the proposed single application rate; total of 6 applications: 2017 g a.i./ha, equivalent to 334% of Canadian maximum annual rate of 603 g a.i./ha), resulted in first-order half-lives and associated $t_{9/10}$ for total toxic residues of 296.3 days and 1028 days, respectively. Total toxic residues are non-persistent to persistent under field conditions, according to the scheme of Goring et al. (1975). A half-life for 1,2,4-triazole was not calculated, but results of the study indicate that it is accumulating and persistent in the environment.

Prothioconazole, prothioconazole-desthio, prothioconazole-*S*-methyl and prothioconazole-thiazocine were not detected in soil below the 30 cm soil depth at any test site soil, while 1,2,4-triazole was not detected below 45 cm in soil. In agreement with laboratory data, modelling studies and the GUS classification, the field results suggest that prothioconazole, prothioconazole-desthio, prothioconazole-*S*-methyl and prothioconazole-thiazocine have a low potential to leach and reach groundwater. 1,2,4-triazole was detected at a lower depth layer than the other compounds (30–45 cm layer), also in agreement with laboratory data indicating a higher mobility for 1,2,4-triazole compared to the other compounds. However, based on the lack of residues detected below 45 cm in soil in field studies, the concern regarding 1,2,4-triazole leaching and reaching groundwater is low.

There is little potential for significant (> 30%) carryover of total toxic residues into the next growing season. Carryover of total toxic residues was 12.6%, 16.4% and 22.4% of the applied prothioconazole at the sites in Manitoba, Saskatchewan and New York, respectively. Prothioconazole alone did not carry over to the next growing season, other than in New York, where 0.5% of the applied parent was attributed to prothioconazole. Prothioconazole was only applied once in Manitoba and Saskatchewan, and the potential exists for greater carryover of total toxic residues than observed at those sites because up to three applications of prothioconazole are proposed on the Canadian label.

5.6 Bioaccumulation

5.6.1 Prothioconazole and Prothioconazole-desthio

The bioconcentration of prothioconazole and of the transformation product prothioconazole-desthio were studied in two separate experiments using the bluegill sunfish (*Lepomis macrochirus*) under flow-through conditions. The data indicate that prothioconazole and prothioconazole-desthio bioconcentrated in bluegill sunfish, but were rapidly metabolized, and all residues were rapidly cleared from fish tissue during depuration.

Prothioconazole concentrations in fish during the uptake phase were variable in both exposure concentrations and did not show a clear accumulation trend in fish tissue. The total residue bioconcentration factor for whole fish was 43.9–57.8 for prothioconazole and 71.6–94.3 for prothioconazole-desthio. For prothioconazole and prothioconazole-desthio only, the steady state whole fish (wet weight) high exposure concentration bioconcentration factors were 19.7 and 65, respectively, which were normalized for 6% lipid content to 18.8 and 45. When exposure ceased, the residues in both studies were depurated, with a half-life of ≤ 0.8 days for whole fish tissues. After 14 days in uncontaminated water, 91–99% of the steady state total residues levels were depurated from whole fish.

[^{14}C]-residues in the fish exposed to prothioconazole were characterized in the metabolism study. Prothioconazole was identified in all fish samples at 40–41% of the total radioactive residues in viscera and at approximately 57% of the total radioactive residues in edible tissues. Prothioconazole-glucuronide was a major transformation product, detected at 15–26% of the total radioactive residues (20–24% in edibles and 15–26% in viscera).

Despite the log K_{ow}s for prothioconazole and prothioconazole-desthio that indicate a potential for bioaccumulation in biological tissue, results show that prothioconazole and its major transformation product prothioconazole-desthio did not bioconcentrate in fish under the test conditions of these studies.

5.6.2 Prothioconazole-*S*-methyl

The log K_{ow} of the transformation product prothioconazole-*S*-methyl is reported by the applicant to be 4.19 (K_{ow} of 15 488). However, a bioconcentration study in fish has not been conducted. Based on the structure similarities between prothioconazole-*S*-methyl, prothioconazole and prothioconazole-desthio, prothioconazole-*S*-methyl is not expected to bioaccumulate in

biological tissue. A bioconcentration factor of 75 has been estimated by the applicant for prothioconazole-*S*-methyl, based on the log K_{ow} and the bioconcentration factor of the parent prothioconazole.

5.6.3 Prothioconazole-thiazocine

The reviewer estimated the log K_{ow} for thiazocine to be 2.9 using the USEPA's KOWWIN software (version 1.67). A bioconcentration study in fish with prothioconazole-thiazocine is not required. Given that prothioconazole-thiazocine was formed by phototransformation only at maximum concentrations of 9.5–14.1%, it is unlikely to be found at > 10% in natural surface water systems.

5.6.4 1,2,4-Triazole

The log K_{ow} of 1,2,4-triazole was not available, but this compound is unlikely to bioaccumulate in biological tissue given its structure. The reviewer estimated the log K_{ow} for 1,2,4-triazole to be -0.76 using the USEPA's KOWWIN software (version 1.67).

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Prothioconazole and the transformation products prothioconazole-desthio and prothioconazole-*S*-methyl have been considered together in a total toxic residue approach. Laboratory studies indicated that hydrolysis and phototransformation of prothioconazole and prothioconazole-desthio in soil are not important routes of transformation in the environment. Prothioconazole is not expected to volatilize from dry or moist surfaces under field conditions based on the vapour pressure and the Henry's law constant. The only soil phototransformation product in laboratory studies was prothioconazole-desthio, formed both in irradiated and dark samples, indicating biotransformation and not photolytic processes. Major aerobic soil biotransformation products were prothioconazole-desthio and prothioconazole-*S*-methyl. Laboratory aerobic soil biotransformation studies indicated that total toxic residues are non-persistent to moderately persistent in aerobic soil (DT_{50}s 3.6–95.2 days).

Major transformation products in terrestrial field dissipation studies were prothioconazole-desthio and 1,2,4-triazole, while prothioconazole-*S*-methyl was a minor transformation product. Field dissipation studies indicated that total toxic residues are non-persistent to persistent under field conditions (DT_{50} of 8.2 days in Manitoba and 111.6 days in Saskatchewan; total toxic residue half-life of 296.3 days in New York). Residues of prothioconazole alone were last detected above LOQ at 7–14 days, depending on the test site. Results show that 1,2,4-triazole accumulates and persists in the environment. Binding to soil could not be tracked as radiolabelled material was not used. Based on the results of terrestrial field studies and the proposed use pattern, significant carryover of total toxic residues to the following growing season is not expected.

The mobility in soil and potential for leaching to groundwater of prothioconazole and of the major transformation products was assessed using laboratory studies, the GUS classification and field studies. Slight to low mobility in soil combined with non-persistence in soil and water and a

GUS classification as a non-leacher indicate prothioconazole is not expected to leach to groundwater. Field dissipation studies further indicate that prothioconazole does not leach, as it was not detected below a 15 cm soil depth. Prothioconazole-desthio is stable to hydrolysis and has high solubility, which is an indicator of soil leaching potential. The low to moderate mobility in soil combined with a GUS classification of non-leacher to borderline leacher indicate a potential for prothioconazole-desthio to leach. However, terrestrial field dissipation studies indicate that it did not migrate below 30 cm under Canadian field conditions; therefore, the concern for leaching of this transformation product is low. Prothioconazole-*S*-methyl is expected to have slight mobility in soil, and it was classified as a non-leacher according to GUS. It was not detected below 30 cm in terrestrial field dissipation studies. 1,2,4-triazole is expected to have moderate to high mobility in soil and is a potential leacher based on its characteristics. However, 1,2,4-triazole was not detected below 45 cm in terrestrial field studies and the concern for leaching is low. Prothioconazole-thiazocine is expected to have high mobility in soil, but it was not detected in terrestrial field dissipation studies.

Conclusions drawn in this review regarding 1,2,4-triazole are supported by information on the fate and behaviour of 1,2,4-triazole in soil published in a review of hexaconazole (PMRA 1995). Previously reviewed data indicated that 1,2,4-triazole is not susceptible to hydrolysis or phototransformation. Microbial action was shown to be important in the transformation of 1,2,4-triazole. Field studies showed that the transformation product was persistent in soil. A high water solubility level and data from laboratory absorption and leaching studies indicated 1,2,4-triazole would be mobile. However, field data showed that, although there was some leaching of 1,2,4-triazole in the soil, 91% of the residues remained in the top 30 cm.

Fate and behaviour of prothioconazole and its major transformation products in the terrestrial environment are summarized in Appendix III, Tables 6 and 7.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

A total toxic residue approach has been used for prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl. The solubility of prothioconazole is pH dependent, with low solubility at acidic pH and very high solubility at basic pH. Hydrolysis of prothioconazole and prothioconazole-desthio is not a route of transformation. UV-absorption data suggest a low potential for phototransformation of prothioconazole and prothioconazole-desthio under environmentally relevant conditions. Prothioconazole together with prothioconazole-desthio have a phototransformation half-life of 19.9 days under continuous irradiation, equivalent to a predicted environmental half-life of 101.9 days in June sunlight.

Major products of phototransformation were prothioconazole-desthio (55.4–55.7%), 1,2,4-triazole (11.9%) and prothioconazole-thiazocine (9.5–14.1%), detected in irradiated samples. Phototransformation is not expected to be a major route of prothioconazole and prothioconazole-desthio transformation in water because the predicted environmental half-life is greater than seven days. Aerobic and anaerobic aquatic biotransformation of prothioconazole was studied in water/sediment systems. Under aerobic and anaerobic conditions, prothioconazole rapidly disappeared from the water, biotransforming as well as partitioning to the sediment, where transformation and binding of residues to the sediment occurred. Major transformation

products in aerobic aquatic systems were prothioconazole-desthio (54.6% of applied parent in the total system), prothioconazole-*S*-methyl (12.7%) and 1,2,4-triazole (41.8%). Total toxic residues are slightly persistent in aerobic aquatic systems (total system DT_{50}: 26.8–41.5 days). A half-life for 1,2,4-triazole could not be calculated, but it is expected to be persistent and accumulate in aerobic aquatic systems. Contrary to aerobic aquatic biotransformation, the only major transformation product in anaerobic aquatic systems was prothioconazole-*S*-methyl (maximum of 78.2% in the total system), which persists in anaerobic aquatic environments. Total toxic residues are persistent under anaerobic aquatic conditions, with a half-life of 1386.3 days.

Prothioconazole and prothioconazole-desthio were bioconcentrated in fish because of their lipophilic properties (Appendix III, Tables 1 and 2), but were rapidly metabolized, and all residues were rapidly cleared from fish tissue (clearance half-lives ≤ 0.8 days). For prothioconazole, the bioconcentration factor for total residues in whole fish was 43.9–57.8, and the steady state whole fish high exposure bioconcentration factor was 19.7 (18.8 when normalized to 6% lipid). For prothioconazole-desthio, the bioconcentration factor for total residues in whole fish was 71.6–94.3, and the steady state whole fish high exposure bioconcentration factor was 65 for (45 when normalized to 6% lipid).

The fate and behaviour of prothioconazole and its transformation products in the aquatic environment is summarized in Appendix III, Tables 8 and 9.

5.9 Expected Environmental Concentrations

As the dissipation of total toxic residues did not follow first-order kinetics, a conservative first-order total toxic residue half-life in soil was estimated at 552.3 days, by dividing the most conservative extrapolated DT_{90} for prothioconazole and prothioconazole-desthio (1833.8 days) by 3.32. For water, the total system total toxic residue half-life was 90.7 days, estimated from the most conservative extrapolated DT_{90} for total toxic residues in aerobic aquatic systems (presented in Appendix III, Table 8).

5.9.1 Soil

Using a scenario in which the maximum Canadian label rate for a single application (201 g a.i./ha) is applied 3 times to bare soil by direct overspray at 10-day intervals and a total toxic residue half-life of 552.3 days, the maximum cumulative application rate is 595.5 g a.i./ha. Assuming a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm, the estimated environmental concentration (EEC) of total toxic residues in soil would be 0.265 mg a.i./kg soil (equivalent to 0.646 mg EP/kg soil).

5.9.2 Aquatic Systems

Screening Level

The screening level EEC in water is based on direct application of a pesticide to a body of water, and is intended to be a simple, conservative and reasonable worst-case estimate of pesticide concentrations in water. The screening level EEC for total toxic residues in water is 0.186 mg/L,

determined assuming a scenario in which prothioconazole is directly applied to a body of water that is 30 cm deep at the maximum cumulative Canadian application rate. Applying prothioconazole directly to water 3 times at 10-day intervals at the maximum single application rate of 201 g a.i./ha using a total toxic residue half-life in water of 90.7 days yields a maximum cumulative Canadian application rate of 559.7 g a.i./ha.

Aquatic Ecoscenario Assessment: Runoff Simulation Level 1
Estimated environmental concentrations for a Level 1 scenario for runoff in a receiving water body for aquatic risk assessment were simulated using the combined Pesticide Root Zone Model and Exposure Analysis Modeling System (PRZM/EXAMS). This water body consists of a 1 ha wetland with an average depth of 0.8 m and a 10 ha drainage area.

Information on application rates and timing was gathered for the major uses of prothioconazole (barley, canola, wheat) as well as for the use with the highest annual application rate (chickpeas). The maximum annual application rate for chickpeas is 0.6 kg a.i./ha (3 applications of 0.2 kg a.i./ha per season). Information gathered on the typical dates of first application for barley, canola, wheat and chickpeas ranged from mid May to the end of July. The starting dates used in the models were from 15 May to 24 July.

EECs of total toxic residues were generated in the aquatic ecoscenario assessment due to the rapid transformation of prothioconazole to prothioconazole-desthio and prothioconazole-*S*-methyl as well as the similar toxicity of the three compounds. Other conservative chemistry and fate input parameters were chosen from among the parent and transformation products. The estimated concentrations are intended to reflect the combined concentration of the three chemicals.

Five geographic scenarios were simulated: a wetland adjacent to barley in the Pacific region, a wetland adjacent to chickpeas and wheat in the Prairies, a wetland adjacent to barley in Ontario, a wetland adjacent to barley in Quebec and a wetland adjacent to a wheat field in the Atlantic region (using a scenario for potatoes in Prince Edward Island). The model simulated 20 years for all scenarios except for the Atlantic region, where it simulated for 57 years.

Appendix III, Table 10, lists the application information and main environmental fate characteristics used in the models.

For each year of the simulation, PRZM/EXAMS calculates both peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the daily concentrations over five time periods (96-hour, 21-day, 60-day, 90-day and 1 year). The 90th percentiles of the peak and the time-averaged concentrations (µg/L) are reported in Appendix III, Table 11.

Level 1 Estimated Environmental Concentrations in Drinking Water Sources
EECs of total toxic residues (prothioconazole and its transformation products prothioconazole-desthio and prothioconazole-*S*-methyl) in potential drinking water sources (groundwater and surface water) were calculated using computer simulation models. EECs of total toxic residues in groundwater were calculated using the Leaching Estimation and Chemistry Model

(LEACHM), which simulates leaching through a layered soil profile over a multi-year period (20 years). The concentrations calculated using LEACHM are estimates of the flux, or movement, of pesticide into shallow groundwater (2 or 5 m depth) with time. EECs of total toxic residues were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir (57-year simulation) and a prairie dugout (81-year simulation).

A Level 1 drinking water assessment was conducted for prothioconazole combined with prothioconazole-desthio and prothioconazole-*S*-methyl, using conservative assumptions with respect to environmental fate, application rate and timing as well as geographic scenario. This Level 1 EEC estimate would, therefore, be expected to allow for future use expansion into other crops at this application rate. The application information and main environmental fate characteristics used in the models are the same as was used in the aquatic ecoscenario modelling (Appendix III, Table 10).

The estimated concentrations of total toxic residues in potential drinking water sources are given in Appendix III, Table 12 and are intended to reflect the combined concentration of all three chemicals.

Level 2 Estimated Environmental Concentrations in Drinking Water Sources

A Level 2 drinking water assessment was conducted because the level of concern was exceeded in the dietary risk assessment when Level 1 EECs were used. Chickpeas were identified as a crop grown almost exclusively in the prairie provinces; therefore, the next highest annual application rate was used (two applications of 0.2 kg a.i./ha per season) for other regions of the country. For the Level 2 assessment, the typical dates of first application were adjusted to be specific for each region.

The combined transformation half-lives were still calculated using the sum of prothioconazole, prothioconazole-desthio prothioconazole-*S*-methyl concentrations at each time interval. However, for Level 2, a recalculated aerobic soil metabolism rate using less conservative criteria was also used (314 days, calculated taking the second highest estimated DT_{90} of 1044 days and dividing by 3.32). The other Level 1 chemistry and fate input parameters, chosen from among the parent and transformation products, remained the same in the Level 2 assessment (Appendix III, Table 10).

The Level 2 EECs of total toxic residues in potential drinking water sources are given in Appendix III, Table 13 and are intended to reflect the combined concentration of all three chemicals.

5.9.3 Vegetation and Other Food Sources

The EECs of total toxic residues in vegetation and food sources were based on the maximum cumulative annual application rate of Proline 480 SC Foliar Fungicide of 292.2 g a.i./ha. This rate was estimated using 3 applications at the maximum single application rate of 201 g a.i./ha applied at 10-day intervals, assuming a combined prothioconazole and prothioconazole-desthio

foliar dissipation half-life of 6.4 days (prothioconazole-*S*-methyl was not measured), calculated using the 90th percentile of half-lives from submitted foliar dissipation studies on wheat, turf grass and peanuts. A direct overspray scenario using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994) for use in ecological risk assessment (Urban and Cook 1986) was used (Appendix III, Tables 14 and 15).

6.0 Effects on Non-target Species

6.1 Effects on Terrestrial Organisms

Results of all the terrestrial toxicity studies reviewed are summarized in Appendix III, Table 1; however, a total toxic residues approach was used for assessment purposes. A summary of the toxicity of prothioconazole and its transformation products is presented hereafter.

The total toxic residues (prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl) and the formulation JAU6476 480 SC generally exhibit low toxicity to terrestrial invertebrates. In acute tests, prothioconazole, prothioconazole-desthio, prothioconazole-*S*-methyl and the formulation JAU6476 480 SC were non-lethal to earthworms at up to 1000 mg/kg dw soil, the highest concentration tested. Sublethal effects of acute exposure included weight loss. Chronic exposure of earthworms to transformation products resulted in effects such as weight loss and a decreased number of offspring per surviving adult. An 11-month study in which the formulation JAU6476 EC 250 was applied 3 times at 200 g a.i./ha did not result in adverse effects on natural earthworm populations. Prothioconazole and the formulation JAU6476 480 SC are relatively non-toxic to the honeybee (*Apis mellifera*) on an acute oral and acute contact basis, according to the classification scheme of Atkins et al. (1981). Prothioconazole and the formulation JAU6476 480 SC were non-lethal to predaceous mites and parasitic wasps. Based on reductions in beneficial capacity smaller than 30%, prothioconazole is classified as harmless to mites up to 225 000 g a.i./ha, while the formulation is harmless to mites and parasitic wasps up to 380 g a.i./ha and 600 g a.i./ha, respectively according to the criteria of the International Organization for Biological Control of Noxious Animals and Plants (Hassan et al. 1994). The formulation was slightly harmful to parasitic wasps at 600 g a.i./ha. Exposure to prothioconazole and prothioconazole-*S*-methyl had no effect on the springtail (*Folsomia candida*), but the number of offspring was reduced following exposure to prothioconazole-desthio.

Overall, prothioconazole and prothioconazole-desthio have minimal toxicity to birds based on studies with bobwhite quails (*Colinus virginianus*) and mallard ducks (*Anas platyrhynchos*). Prothioconazole and prothioconazole-desthio are practically non-toxic to birds on an acute oral according to the classification schemes of the USEPA (1985a). Sublethal effects of acute exposure included reduced feed consumption and diarrhea (male bobwhite quails only). On an acute dietary basis, prothioconazole was practically non-toxic to bobwhite quails and mallard ducks, but prothioconazole-desthio was slightly toxic to bobwhite quails, according to the USEPA classification scheme (USEPA 1985b). While dietary exposure to prothioconazole had no effect on the mallard duck, effects of dietary exposure to prothioconazole observed in the bobwhite included intestinal inflammation, and effects of dietary exposure to prothioconazole-desthio included mortality, reduced vigilance, weight loss and reduced food consumption. The

reproductive toxicity of prothioconazole was studied in both the bobwhite quail and the mallard duck; no parental or reproductive toxicity effects were observed in any study.

Total toxic residues are practically non-toxic to small wild mammals, according to the classification schemes of the USEPA (1985c). Effects observed in two-generation reproduction studies with rats exposed to prothioconazole and prothioconazole-desthio via gavage included reduced body weight and body-weight gain in parents, F_1 adults and pups of both generations, decreased pup viability, a decreased number of estrous cycles in both the parental and the F_1 generation as well as an increased length of the estrous cycle in parental adults. A reproduction and development study on rabbits exposed to prothioconazole via gavage indicated that the compound was teratogenic at non-maternally toxic doses. Maternal effects included decreased body weight, while developmental effects included decreased fetal weights, microphthalmia (small eyes), incomplete or unossified digits, toes, sternebrae and pubic bone as well as pubic bone dysplasia.

The effect of JAU6476 480 SC on seedling emergence and vegetative vigour of vascular plants was assessed on 6 dicot species and 4 monocot species at a concentration of 305 g a.i./ha. Inhibition greater than 25% on was observed in only one dicot (cucumber: *Cucumis sativa*) in the seedling emergence study, while effects greater than 25% on vegetative vigour were not observed in any species. A Tier II seedling emergence study was conducted with cucumbers, but no treatment-related effects were observed up to 305 g a.i./ha, the highest concentration tested.

1,2,4-Triazole

No toxicity studies were submitted for 1,2,4-triazole. A published review for another active ingredient, hexaconazole, indicates that the transformation product 1,2,4-triazole is non-toxic to earthworms (14-day lethal concentration 50% [LC_{50}] > 1000 mg a.i./kg) (PMRA 1995).

6.2 Effects on Aquatic Organisms

The toxicity of prothioconazole and its transformation products to aquatic organisms is summarized in Appendix III, Table 17.

Total toxic residues are moderately toxic to freshwater organisms and slightly to moderately toxic to estuarine/marine organisms on an acute basis, in accordance with USEPA descriptive classifications (USEPA 1985d, 1985e, 1985f, 1985g, 1985h). Total toxic residues were toxic to freshwater and marine algae as well as to aquatic vascular plants at low concentrations.

In general, the acute toxicity of the formulation JAU6476 480 SC is similar to that of the parent prothioconazole. The most sensitive freshwater organism was duckweed (*Lemna gibba*) with a 96-hour no observed effect concentration (NOEC) of 0.00334 mg a.i./L, based on effects on frond numbers and biomass. The most sensitive estuarine/marine organism was the saltwater diatom *Skeletonema costatum*, with a 96-hour NOEC of 0.00448 mg a.i./L based on effects on cell density. These endpoints were selected for the risk assessment and for determining buffer zones to protect freshwater and estuarine/marine habitats.

On a chronic basis, prothioconazole and prothioconazole-desthio were toxic to freshwater and marine invertebrates, including daphnids, midges and saltwater mysids. No chronic studies were submitted with prothioconazole-*S*-methyl. Effects observed in daphnids included adult mortality, reduced growth (total length), reduced number of offspring and reduced number of offspring per parent per reproduction day. Emergence, mean development time and mean development rate were affected in the midge, while the number of offspring per reproductive day was reduced in the saltwater mysid. No acceptable early life-stage toxicity studies were available to determine the effects of prothioconazole or prothioconazole-desthio on the early life stages of freshwater fish; however, an acceptable full life-cycle toxicity study in fish exposed to prothioconazole-desthio was available. Exposure of the fathead minnow to prothioconazole-desthio over a full life cycle resulted in adverse effects on first-generation larval/juvenile survival, juvenile (eight-weeks posthatch) and male growth, spawning frequency as well as in morphological deformities.

1,2,4-Triazole

No toxicity studies were submitted for the transformation product 1,2,4-triazole. Information obtained from the published review of hexaconazole, another active ingredient, indicate that 1,2,4-triazole was non-toxic to *Daphnia magna* (24-hour LC_{50} 900 mg/L) and rainbow trout (*Oncorhynchus mykiss*; 96-hour LC_{50} 533 mg/L), but toxic to the freshwater green alga (*Scenedesmus subspicatus*; 5-day effect concentration 50% [EC_{50}] of 1.5 mg/L, reviewer-calculated and based on measured concentrations) (PMRA 1995). 1,2,4-Triazole will not be considered further in the risk assessment because relevant concentrations or endpoints cannot be determined; it may be addressed in the future, considering multiple inputs.

6.3 Effects on Biological Methods of Sewage Treatment

Not required.

6.4 Risk Characterization

Risk assessment integrates the environmental exposure and ecotoxicology data to estimate the potential for adverse ecological effects. The PMRA currently conducts a deterministic risk assessment of pest control products. Environmental risk is characterized using the risk quotient (RQ) method, which is the ratio of the expected environmental concentration (EEC) divided by the toxicity endpoint. The EECs used to calculate the RQ are described in Section 5.9 and captured in Appendix III, Tables 11, 13, 14 and 15. The toxicity endpoint generally used is the NOEC (or no observed effect level [NOEL]; if a NOEC or NOEL is not available, one-tenth of the lethal concentration 50% [LC_{50}] or LD_{50} is used to approximate a no-effect level) or an effect concentration 25% (EC_{25}; for terrestrial plants). Risks are then classified based on the scheme presented in Appendix III, Table 18.

In addition to the RQ, an indicator of risk in birds and mammals is the number of feeding days on contaminated food required to reach the toxicity endpoint of concern (acute oral toxicity NOEL). Risk based on the number of feeding days is classified as follows: if the number of feeding days is less than one, then there is a risk, and, conversely, if the number of feeding days is greater than or equal to one day, then there is negligible risk (days < 1 = risk; days ≥ 1 = negligible risk).

Toxicity studies were submitted for prothioconazole, prothioconazole-desthio, prothioconazole-*S*-methyl and the formulation JAU6476 480 SC. Given the complexities associated with the fate, transport and toxicity of prothioconazole in the environment, a total toxic residues approach was used to evaluate the potential risks of prothioconazole and its transformation products prothioconazole-desthio and prothioconazole-*S*-methyl.

6.4.1 Environmental Behaviour

In the terrestrial environment, prothioconazole rapidly transforms by aerobic soil biotransformation. Binding to soil is also likely a critical component of prothioconazole's fate in soil. Major soil transformation products are prothioconazole-desthio, prothioconazole-*S*-methyl and 1,2,4-triazole. Total toxic residues (prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl) are non-persistent to persistent under field conditions, and significant carryover of total toxic residues into the next growing season is not expected. Prothioconazole is expected to have low mobility in soils, prothioconazole-desthio has low to moderate mobility, prothioconazole-*S*-methyl has slight mobility, and 1,2,4-triazole has moderate to high mobility in soils. Based on mobility, prothioconazole-desthio and prothioconazole-*S*-methyl have low potential to leach to groundwater, while 1,2,4-triazole has a higher potential to reach groundwater. Field dissipation studies indicated that below a soil depth of 30 cm, residues were at or less than the LOQ. On the other hand, 1,2,4-triazole was detected up to 45 cm in depth at levels below the LOQ.

In the aquatic environment, prothioconazole rapidly dissipates from the water through biotransformation as well as partitioning to the sediment, where biotransformation and binding of residues to the sediment occurs. The major transformation products in the aerobic aquatic environments are prothioconazole-desthio, prothioconazole-*S*-methyl and 1,2,4-triazole. The total toxic residues are slightly persistent in aerobic aquatic environments and persistent in anaerobic aquatic environments.

6.4.2 Terrestrial Organisms

The risk characterization to terrestrial organisms is summarized in Appendix III, Table 19.

Earthworms
Using the acute NOECs for earthworms and the EEC in soil (Section 5.9.1), the risk of acute exposure of earthworms to total toxic residues is negligible at the proposed application rates (RQs << 0.1). The risk of chronic exposure of earthworms is negligible to low at the proposed maximum cumulative application rate.

Honeybees
According to the classification system of Atkins et al. (1981), prothioconazole and the end-use product JAU6476 480 SC are relatively non-toxic to bees on both an acute contact and acute oral basis. According to Atkins et al. (1981), the LD_{50} in micrograms per bee (µg/bee) can be converted to the equivalent application rate in kg/ha by multiplying µg/bee by 1.12. Therefore, the field LD_{50}s range from > 79.5 to > 106.5 kg a.i./ha, significantly higher than the proposed maximum cumulative application rate of 292.2 g a.i./ha on vegetation and other food sources

(Section 5.9.3). The risk to honeybees resulting from acute oral or contact exposure to prothioconazole and the end-use product is negligible.

Predators and Parasites

According to evaluation criteria of the International Organization for Biological Control of Noxious Animals and Plants (Hassan et al. 1994) and as discussed in Section 6.1, prothioconazole and the formulation JAU6476 480 SC were considered harmless to parasitic wasps and predaceous mites at levels up to and exceeding the proposed Canadian maximum cumulative application rate of 292.2 g a.i./ha for vegetation and other food sources (Section 5.9.3).

Terrestrial Arthropods

Using the no observed effect rate (NOER) and the EEC for total toxic residues in soil of 0.265 mg/kg soil (Section 5.9.1), the risk quotients are all << 0.1, indicating that the total toxic residues pose a negligible risk to the reproduction of springtails (*Folsomia candida*) at the proposed application rates.

Wild Birds

Wild upland game birds and waterfowl, as represented by northern bobwhite quail and mallard duck, respectively, could be exposed to residues of prothioconazole and its transformation products as a result of consumption of treated vegetation, contaminated prey or spray drift. The EECs of prothioconazole and transformation products in the diets of the bobwhite quail and mallard duck were 51.1 and 9.9 mg/kg dry weight of diet, respectively (Appendix III, Table 15).

The acute oral risk to birds was assessed for total toxic residues, based on the number of feeding days required by a bobwhite quail to reach the toxicity endpoints (LD_{50} and NOEL). The number of feeding days were determined using the toxicity endpoint (LD_{50} or NOEL) and EEC for total toxic residues as well as the food consumption (FC) and body weight per individual (BWI) based on the respective studies (FC: prothioconazole study 0.0172 kg/ind/day, prothioconazole-desthio study 0.0228 kg/ind/day; BWI: prothioconazole study 0.240 kg bw/ind, prothioconazole-desthio study 0.182 kg bw/ind). The predicted daily intake of residues (DI = FC × EEC) was estimated as 0.879 mg a.i./ind/day for the prothioconazole study and 1.057 mg a.i./ind/day for the prothioconazole-desthio study. The LD_{50} per individual (LD_{50} × BWI) was estimated as > 480 mg a.i./ind for the study with prothioconazole and 364 mg a.i./ind for the study with prothioconazole-desthio. The NOEL per individual (NOELind = NOEL × BWI) was estimated for prothioconazole as 480 mg a.i./ind based on mortality and 48.0 mg a.i./ind based on diarrhea, and for prothioconazole-desthio as 182 mg/ind based on mortality and 91.1 mg/ind based on clinical signs of toxicity and weight reduction.

The number of feeding days required to reach the LD_{50} (days = LD_{50} ind/DI) and the NOEL (mortality) toxicity endpoint (days = NOELind/DI) was estimated at ≥ 312 days and ≥ 156 days, respectively, for total toxic residues. The number of feeding days required to reach the concentration of total toxic residues where sublethal effects were observed in the laboratory as a result of acute oral exposure was ≥ 54.6 days. Risk of mortality or of sublethal effects such as diarrhea, weight reduction or clinical signs of toxicity from acute oral exposure to total toxic residues is negligible.

The acute dietary and chronic reproductive risk to birds was assessed using the NOEC and EEC for each species and exposure. Based on the RQ values for bobwhite quail and mallard duck (all < 0.05), the acute dietary risk and the chronic reproductive risk to birds is expected to be negligible.

Small Wild Mammals

Wild mammals could be exposed to residues of prothioconazole or its transformation products as a result of consumption of sprayed vegetation and/or contaminated prey. The EECs of total toxic residues in the diets of rat and mouse were 147.4 and 146.5 mg a.i./kg dry weight of diet, respectively (Appendix III, Table 15).

The acute oral risk to rats and mouse was assessed for total toxic residues and the formulation JAU6476 480 SC, based on the number of feeding days required to reach the toxicity endpoint (NOEL). Default values were used for food consumption (rat 0.060 kg dw/ind/day, mouse 0.006 kg dw/ind/day) and body weight (rat 0.35 kg bw/ind, mouse 0.033 kg bw/ind) (USEPA 1988). The predicted daily intake of total toxic residues (DI = FC × EEC) was estimated (rat: 8.84 mg/ind/day; mouse: 0.879 mg/ind/day), and the NOEL per individual (NOELind = NOEL × BWI) was estimated (rat: prothioconazole and formulation 2170 mg a.i./ind; prothioconazole-desthio 350 mg/ind; prothioconazole-*S*-methyl 700 mg/ind; mouse: prothioconazole-desthio 16.5 mg/ind). The number of feeding days required to reach the toxicity endpoint (days = NOELind/DI) was estimated to be between 32.1 days and 245 days for a rat and 18.8 days for a mouse. Acute risk to the rat and mouse from consumption of prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl residues is considered negligible.

The reproductive risk to small mammals was assessed based on rat multigeneration reproductive studies. For prothioconazole, risk to the parents (decreased body weight and body-weight gain, decreased number of estrous cycles and increased length of estrous cycles; in F_1 generation decreased weight gain and body-weight gain and decreased number of estrous cycles) and offspring (body-weight loss in F_1 and F_2 pups) was low (EEC/NOEC = 147.37/583.3 = 0.25). For prothioconazole-desthio, risk to reproduction (decreased pup viability and pup body weight) was low.

The chronic developmental and neurotoxicity risk to mammals was assessed using the NOEC and EEC for each species and exposure. Based on the RQ values for the reproduction and developmental neurotoxicity studies with prothioconazole-desthio in the rat and the rabbit, the chronic developmental and neurotoxicity risk to mammals is expected to be moderate (RQ = 2.99–3.34).

This estimate of risk is conservative as it assumes that the animals are consuming 100% diet contaminated with the maximum concentration of residues expected immediately after application for an exposure period of approximately 36 days (from gestational day 6 to lactational day 21, with gestation lasting approximately 21 days). Considering the length of the exposure period, the probable decline in total toxic residue levels in the food items over time, and the unlikelihood that the diet of the animals will consist entirely of contaminated food over a 36-day period, the concern of developmental and neurotoxic effects in mammals is low.

Terrestrial Vascular Plants
Toxicity to the cucumber (*Cucumis sativa*, Cucurbitaceae) was observed in a seedling emergence study. Shoot height and dry weight of cucumber were reduced when exposed to the formulation JAU6476 480 SC at a rate of 305 g a.i./ha. No significant effects on vegetative vigour were observed in plants at 305 g a.i./ha, the highest rate of JAU6476 480 SC tested. An EC_{25} of 305 g a.i./ha was used for seedling emergence and for vegetative vigour due to lack of data testing the effects of exposure to higher concentrations of prothioconazole. Based on the total annual rate of 603 g a.i./ha, the RQ (EEC/EC_{25}) was 1.95 for seedling emergence and for vegetative vigour, indicating a moderate risk to terrestrial plants at the proposed total annual application rate. It has been determined that terrestrial buffer zones are not required to protect terrestrial vascular plants from spray drift from ground or aerial application.

6.4.3 Aquatic Organisms

6.4.3.1 Screening Level

As previously discussed, aquatic toxicity was studied with the active ingredient prothioconazole, the transformation products prothioconazole-desthio and prothioconazole-*S*-methyl and the formulated product JAU6476 480 SC. Aquatic organisms can be exposed to prothioconazole and its transformation products as a result of drift and runoff. To assess the potential for effects from exposure to prothioconazole and its transformation products, a screening level EEC for total toxic residues in the aquatic environment (prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl) based on a direct application to water was used as the exposure estimate (0.186 mg/L). This assessment identifies those uses that do not pose a risk and identify the taxonomic groups at risk. In those cases where RQ > 1, a Level 1 assessment was conducted to determine risk resulting from runoff and/or drift.

The screening level risk characterization to aquatic organisms is summarized in Appendix III, Table 20.

Freshwater Invertebrates
Using the acute and chronic NOECs and the screening level EEC, the threshold of effects was not exceeded for acute exposure of freshwater invertebrates, but was exceeded for chronic exposure of daphnids.

Freshwater Fish
The initial assessment using the screening level EEC for total toxic residues and the appropriate NOEC indicates that the threshold of effects is not exceeded for acute exposure of freshwater fish, but is exceeded for chronic exposure.

Freshwater Algae and Aquatic Vascular Plants
Using NOECs or one tenth the EC_{50} where no NOEC was available, an initial assessment using the screening level EEC for total toxic residues indicates that the threshold of effects was exceeded for freshwater diatoms, green algae and the aquatic vascular plant duckweed.

Estuarine/Marine Organisms
Using the appropriate NOECs for studies conducted with prothioconazole and prothioconazole-desthio as well as the screening level EECs for total toxic residues, the threshold of effects was not exceeded except for the marine invertebrate mysid shrimp exposed to prothioconazole-desthio on an acute and chronic basis.

It should be noted that results of two acceptable acute and chronic toxicity studies on the saltwater mysid using prothioconazole-desthio indicate that lethal (LC_{50}) and sublethal (NOEC) effects occur at more or less the same concentration. Based on the proposed use pattern, the potential for estuarine/marine exposure is small. In addition, estuarine/marine environments are characterized by large and dynamic volumes of water; it is highly likely that any amount of chemical that reaches the estuarine environment will dissipate quickly. Although the validity of the results of the acute and chronic studies conducted with prothioconazole-desthio on the saltwater mysid shrimp could be questioned, new studies are not required.

6.4.3.2 Level 1 Aquatic Risk Assessment

6.4.3.2.1 Assessment of the Potential Risk From Drift

The percentage of drift required to reach an EEC in water equivalent to the concentration resulting in effects to aquatic organisms is estimated as the inverse of the RQ from direct overspray multiplied by 100 (1/RQ × 100%).

In a body of water that is 30 cm deep, the amount of drift required to reach an EEC equivalent to the concentration resulting in effects to the most sensitive aquatic organism (*Lemna gibba*, NOEC = 0.00334 mg a.i./L) is 1.8% (= 1/55.7 × 100%). The amount of drift required to reach an EEC in an 80-cm deep body of water that is equivalent to the concentration resulting in effects to the most sensitive aquatic organism is 4.8% (EEC in 80 cm of water from direct overspray is 0.07 mg/L; therefore, 1/(0.07/0.00334) × 100% = 4.8%).

Buffer zones will be calculated to reduce the potential acute or chronic risk to aquatic organisms from ground and aerial spray.

6.4.3.2.2 Assessment of Potential Risk From Runoff

The Level 1 total toxic residue EECs in a 1-ha receiving water body adjacent to the spray field were predicted by PRZM/EXAMS and are presented in Appendix III, Table 11. The PRZM/EXAMS values are 90th percentile concentrations of the concentrations determined at a number of time frames including the yearly peak as well as the 96-hour, 21-day, 60-day, 90-day and yearly averages. Following the screening level risk assessment for aquatic organisms, the level of concern for acute effects in freshwater and marine algae, freshwater vascular plants and marine invertebrates was exceeded as well as for chronic effects in freshwater and marine invertebrates and freshwater fish. To better characterize the risk, the risk from exposure to run off into a body of water adjoining to the application field was determined using the runoff 90th percentile of the EECs predicted by PRZM/EXAMS for appropriate time frames in five regions of Canada.

The risk of effects to freshwater organisms from exposure to prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl from runoff is provided in Appendix III, Table 21.

Freshwater Invertebrates
The total toxic residue EECs considered were the 90th percentile 21-day concentrations as the studies were conducted for 21 days. Using the chronic NOEC, the risk to freshwater invertebrates (*Daphnia magna*) from chronic exposure to prothioconazole and its transformation products from runoff is negligible to low.

Freshwater Fish
The EECs considered were the 90th percentile yearly average concentrations, as the fish life-cycle study was conducted for a period of 9 months. Using the chronic NOEC, the risk to freshwater fish (fathead minnow, *Pimephales promelas*) from chronic exposure to prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl combined, through runoff is negligible.

Freshwater Algae
The risk to the green alga *Scenedesmus subspicatus* from exposure to prothioconazole and its transformation products through runoff is low in all examined regions of Canada. Using the NOEC, moderate risk to the freshwater diatom *Navicula pelliculosa* was identified in the Prairies, Ontario and the Atlantic Region from exposure to prothioconazole and transformation products at predicted EECs in bodies of water adjoining the spray field (RQs of 1.1–1.6). The EECs considered were the 90th percentile 96-hour concentrations as the studies were conducted for 96 hours.

Aquatic Vascular Plants
Using the NOECs, a moderate risk to duckweed, *Lemna gibba*, was identified in all examined regions of Canada at predicted total residue EECs in bodies of water adjoining the spray field (RQs of 1.3–5.9). Given the study durations of 7 days, the EECs considered were the 90th percentile 96-hour concentrations, as they were slightly more conservative than the 90th percentile 21-day concentrations obtained through modelling.

Marine Invertebrates
Using the acute and chronic NOECs, the risk of acute and chronic effects to the saltwater mysid shrimp (*Mysidopsis bahia*) from exposure to prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl from runoff is low in all examined regions of Canada. The EECs considered were the 90th percentile 96-hour concentrations for the acute risk and the 90th percentile 21-day concentrations for the chronic risk, as they correspond to the period of time the studies were conducted.

Marine Algae
Using the NOEC, a moderate risk to the marine diatom (*Skeletonema costatum*) was identified in all relevant regions of Canada from exposure to prothioconazole and transformation products prothioconazole-desthio and prothioconazole-*S*-methyl at predicted EECs in bodies of water adjoining the spray field (RQs of 1.3–5.9). The EECs considered were the 90th percentile 96-hour concentrations, as this time period corresponds to the study duration.

6.4.3.2.3 Further Characterization of Risk

To further characterize the risk of effects from exposure through runoff identified for freshwater diatoms, aquatic vascular plants and saltwater diatoms, the total toxic residue EECs predicted in bodies of water were compared to the concentrations causing effects in populations (EC_{25} and EC_{50}).

The total toxic residue EECs predicted in the Prairies, Ontario and the Atlantic Region are lower than the concentration that would cause a 25% effect in freshwater diatoms (*Navicula pelliculosa*; EC_{25} = 0.0504 mg/L, based on biomass), duckweed (*Lemna gibba*; EC_{25} = 0.0137 mg/L, based on weight, in study with prothioconazole-desthio) and saltwater diatom (*Skeletonema costatum*; EC_{25} = 0.00853 mg/L, based on biomass) populations. The total toxic residue EECs are all lower than the concentrations causing effects of 50% in populations of these organisms. The risk of effects to freshwater and marine diatoms as well as to duckweed from exposure to total toxic residues via runoff generally lies between the NOEC and the EC_{25}. Considering the resilient nature of algae and aquatic vascular plants and, for saltwater diatoms, the low potential for estuarine/marine exposure based on the proposed use pattern, the level of concern for the risk of negative effects to these organisms from exposure to total toxic residues (prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl) is low.

6.4.4 Uncertainty Regarding Risk to Early Life Stages of Fish and Amphibians

Toxicity endpoints from early life-stage toxicity studies may serve to estimate the potential risk to amphibians. No early life-stage toxicity study in fish was available for prothioconazole or prothioconazole-desthio. Prothioconazole is expected to rapidly transform in water; therefore, an early life-stage toxicity study would likely not be required for this compound. A full life-cycle toxicity study with the fathead minnow was, however, available for prothioconazole-desthio.

Had the NOEC, based on malformations, from an unacceptable early life-stage toxicity study with fish using prothioconazole-desthio been used (the study found unacceptable due to poor hatching success and fertilization rate in the controls), a moderate chronic risk to early life stages of fish (and potentially to amphibians) would have been identified. It should be noted that a chronic risk was not identified in the full life-cycle study with fish, possibly due to varying sensitivities between species.

As an acceptable full life-cycle study with prothioconazole-desthio is available, a new early life-stage toxicity study with prothioconazole-desthio is not required. However, considering the difference in results between the acceptable life-cycle test and the unacceptable early life-stage study, it is uncertain the fish in early life stages, and potentially amphibians, are at risk. Buffer zones are normally generated to mitigate drift in bodies of water 80 cm deep during a Level 1 runoff assessment. However, to err on the side of safety and to provide protection to fish at early life stages and to amphibians, which are commonly found in shallow bodies of water, it is recommended that buffer zones be generated to mitigate drift in bodies of water 30 cm deep.

6.5 Risk Mitigation

An assessment of the environmental safety associated with prothioconazole and the end-use product Proline 480 SC Foliar Fungicide at the maximum annual application rate of 603 g a.i./ha has been conducted. The following environmental risks were identified.

Aquatic Organisms
Proline 480 SC Foliar Fungicide may pose a risk to the following aquatic organisms:

- freshwater vascular plants (e.g., *Lemna gibba*)
- freshwater algae (e.g., diatom, *Navicula pelliculosa*)
- marine algae (e.g., diatom, *Skeletonema costatum*)

Buffer zones to protect sensitive aquatic habitats from spray drift are recommended to mitigate risk.

Due to the uncertainty associated with the toxicity to early life stages of fish and to amphibians, it is recommended that buffer zones for aquatic habitats less than 1 m deep be generated for bodies of water 30 cm deep instead of 80 cm, as generally done when a Level 1 runoff assessment is conducted, to err on the side of safety and to be protective of early life stages of fish and amphibians. Buffer zones are normally generated to mitigate drift in bodies of water 80 cm deep during a Level 1 runoff assessment. However, to err on the side of safety and to provide protection to fish at early life stages and to amphibians, which are commonly found in shallow bodies of water, it is recommended that buffer zones be generated to mitigate drift in bodies of water 30 cm deep.

Method of Application	Crop	Buffer Zones (metres) Required for the Protection of Aquatic Habitat of Depths:		
		< 1 m	1–3 m	> 3 m
Field sprayer	All listed crops	2	1	0
Aerial (fixed and rotary wing)	Canola	10	0	0

6.5.1 Labelling Statements

The following label statements are recommended to mitigate the risk to aquatic organisms:

> TOXIC to aquatic organisms. Observe buffer zones specified under **DIRECTIONS FOR USE**.

DO NOT apply this product directly to freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, ditches and wetlands), estuaries or marine habitats. **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. **DO NOT** allow nozzle spacing to exceed 65% of boom length.

Buffer Zones:

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, wetlands and estuarine/marine habitats).

Method of application	Crop	Buffer Zones (metres) Required for the Protection of Aquatic Habitat of Depths:		
		< 1 m	1–3 m	> 3 m
Field sprayer	All listed crops	2	1	0
Aerial (fixed and rotary wing)	Canola	10	0	0

Surface Runoff

Currently, no methods are available for mitigating the impacts of pesticide transport in surface runoff. There are, however, precautionary measures that should be included on product labels to minimize the risk of aquatic contamination from surface runoff. The following precautionary measures are recommended for placement on the label:

To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to, heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g., soils that are compacted or fine-textured such as clay).

Avoid application of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

7.0 Efficacy

7.1 Effectiveness Against Target Organisms or With Respect to the Effect Achieved

7.1.1 Intended Uses

Barley
For suppression of fusarium head blight, apply Proline at 315–420 mL/ha (150–200 g a.i./ha), once per season. For control of the following foliar diseases: net blotch (*Pyrenophora teres*), scald (*Rhynchosporium secalis*) and spot blotch (*Cochliobolus sativus*), apply once per season at 210–315 mL/ha (100–150 g a.i./ ha). A maximum of two applications per season of Proline may be made to cereal diseases (one for fusarium head blight, and one for foliar diseases). Apply with a non-ionic surfactant, AgSurf or Agral 90 at 0.125% v/v. Do not apply within 30 days of harvest. Applications may be made by ground spray equipment.

Wheat (spring, durum and winter)
For suppression of fusarium head blight and control of Septoria glume blotch (*Stagonosora nodoru*), apply Proline once at 315–420 mL/ha (150–200 g a.i./ha). For control of the following foliar diseases: Septoria leaf blotch (*Septoria tritici*), tan spot (*Pyrenophora tritici-repentis*) and leaf rust (*Puccinia recondita*), apply once at 315 mL/ha (150 g a.i./ha). A maximum of two applications per season of Proline may be made to cereal diseases (one for fusarium head blight, and one for foliar diseases). Apply with a non-ionic surfactant, AgSurf or Agral 90 at 0.125% v/v. Do not apply within 30 days of harvest. Applications may be made by ground spray equipment.

Canola (*Brassica napus*), Rapeseed (*Brassica rapa*) and Oriental mustard (oilseed types—*Brassica juncea*)
For control of Sclerotinia stem rot (*Sclerotinia sclerotiorum*), apply Proline at 315–420 mL/ha (150–200 g a.i./ha). A maximum of two applications per season of Proline may be made. Apply with a non-ionic surfactant, AgSurf or Agral 90 at 0.125% v/v. Do not apply within 36 days of harvest. Applications may be made by ground or aerial spray equipment.

Chickpeas and Lentils
For control of Ascochyta blight (*Ascochyta* spp.), apply Proline at 315–420 mL/ha (150–200 g a.i./ha). A maximum of three applications per season of Proline may be made. Apply with a non-ionic surfactant, AgSurf or Agral 90 at 0.125% v/v. Repeat applications as needed using a 10- to 14-day spray interval if conditions remain favourable for continued or increasing disease development. Applications may be made by ground or aerial spray equipment. Allow a minimum of 7 days from the last application until cutting or swathing the crop for harvest.

7.1.2 Mode of Action

Prothioconazole belongs to the Group 3 Fungicides; specifically it is a triazole, falling into the DMI class of SBIs (SBI: Class 1). There are 24 other fungicidal active ingredients within the same class as prothioconazole (Group 3 Fungicide, C14 SBI - Class 1, DMI, triazole). The mode of action is to inhibit the demethylation process at position C14 of the lanosterol or 2,4-methylene dihydrolano-sterol, both of which are precursors of sterols in fungi.

According to the Fungicide Resistance Action Committee (FRAC), there are great differences in the activity spectra of the different DMI fungicides, and resistance is known in various strains of fungi. It is accepted that cross resistance is present between fungicides active against the same fungus. However, it is also believed that the SBI Class 1 DMI fungicides show no cross resistance to other classes of SBI fungicides. Prothioconazole is rated as having a medium risk for resistance developing in a fungal population, in general.

7.1.3 Crops

Proline 480 SC Foliar Fungicide is proposed for use on the following crops: wheat (spring, durum and winter), barley, canola, rapeseed, Oriental mustard (oilseed type), chickpeas and lentils.

7.1.4 Effectiveness Against Pest

7.1.4.1 Wheat

Seventy-two studies were conducted in Manitoba, Ontario, Saskatchewan, North Dakota and Ohio between 2001 and 2005. Eight winter varieties, fourteen spring varieties and four durum varieties were tested. For all efficacy trials, one application was made at 100, 150, 175 and 200 g a.i./ha with a non-ionic surfactant, AgSurf or Induce, timed from flag leaf to full flowering stage. The trials compared the application rates and timing.

Fusarium Head Blight
Twenty-four fusarium head blight studies demonstrated that Proline provided adequate suppression of fusarium head blight severity and incidence, with an average of 75% severity reduction and 68% incidence reduction. However, the main concern of fusarium head blight infection is the grain contamination with mycotoxin deoxynivalenol (DON) which reduces wheat quality. The data showed that the proposed high rate consistently provided higher DON reduction with an average of 89% at 200 g a.i./ha versus 68% at the lower rates. The data also showed that Proline provided higher DON reduction than the commercial standard Folicur. Therefore, the proposed rate range of 150 to 200 g a.i./ha is supported.

Septoria Glume Blotch
The Septoria glume blotch studies demonstrated that Proline provided adequate disease control at the proposed rate of 150–200 g a.i./ha The data also showed that Proline provided similar disease severity and disease incidence control compared to the commercial standards Tilt and Bravo.

Septoria Leaf Blotch
Thirteen Septoria leaf spot studies demonstrated that Proline provided adequate disease control at the rate of 150 g a.i./ha. The data also showed that Proline provided similar disease severity and disease incidence control compared to the commercials standards Folicur, Tilt, Bravo, Stratego and Headline.

Tan Spot
Six tan spot studies demonstrated that Proline provided adequate disease control at the rate of 150 g a.i./ha. The data also showed that Proline provided similar disease severity and disease incidence control compared to the commercial standards: Folicur, Tilt, Stratego and Headline.

Leaf Rust
Fifteen leaf rust studies demonstrated that Proline provided adequate disease control at the rate of 150 g a.i./ha. The data also showed that Proline provided similar disease severity and disease incidence control compared to the commercial standards Folicur, Tilt, Stratego, Flint and Headline.

7.1.4.2 Barley

Forty-two studies were conducted in Manitoba, Ontario, Quebec, Idaho, North Dakota and Minnesota between 2001 and 2005; 1 winter variety and 10 spring varieties were tested. For all efficacy trials, 1 application was made at 100, 150, 175 or 200 g a.i./ha with a non-ionic surfactant, AgSurf or Induce, timed from flag leaf up to 3 days after full head. The trials compared the application rates and timing.

Fusarium Head Blight
Seven fusarium head blight studies demonstrated that the Proline application numerically reduced the fusarium head blight severity and incidence, with an average of 55.5% disease severity reduction and 31.7% disease incidence reduction. The data also demonstrated that Proline application reduced the grain contamination with DON. The data showed a positive response to increased rates of Proline, an average of 48.6%, 59.4% and 63.5% DON reduction for the 150, 175 and 200 g a.i./ha rates, respectively. Therefore, it is recommended that the high rate of Proline (200 g a.i./ha) be applied under heavy disease pressures.

Six studies compared the application timing from BASF, Bayer, Ciba-Geigy and Hoechst (BBCH) growth stage 51 to 59. The data showed a trend of the later the application, the higher the DON reduction. This suggests that applying the product later than what is proposed may result in higher DON reduction. However, Canadian barley varieties are closed-flowering types, which means they flower while the head is still in the boot. As such, barley is most susceptible to fusarium head blight infection when the head emerges from the boot, although infection can occur any time between heading and maturity. Therefore, the proposed timing, when 70% to 100% of the main stem heads are fully emerged to three days after full head emergence, is supported.

Scald
Seven scald studies demonstrated that Proline provided adequate disease control at the proposed rates of 100–150 g a.i./ha The data also showed that Proline provided similar disease severity and disease incidence control compared to the commercial standards Tilt and Stratego.

Spot Blot
Six spot blot studies demonstrated that Proline provided adequate disease control at the rates of 100–150 g a.i./ha. The data also showed that Proline provided similar disease severity and disease incidence control compared to the commercials standards Tilt, Stratego and Headline.

Net Blotch
Thirteen net blotch studies demonstrated that Proline provided adequate disease control at the rate of 100 g a.i./ha. However, data also support the claim for control of scald and spot blotch at 100–150 g a.i./ha. The higher rate (150 g a.i./ha) for control of net blotch is supported because the product is applied preventatively, and the timing for these three foliar diseases is almost the same. The data also showed that Proline provided similar disease severity and disease incidence control compared to the commercial standards Tilt, Stratego and Headline.

7.1.4.3 Canola, Rapeseed and Oriental Mustard (oil-type)

Eight small-scale, ground application trials were conducted in Manitoba and North Dakota from 2000 to 2003 to test Proline for control of Sclerotinia stem rot in canola and rapeseed. Two aerial application trials were conducted in North Dakota in 2003 to demonstrate the product will maintain efficacy if applied by this method. Five varieties of summer canola were tested, and two varieties of summer rape were tested. For all trials, applications were made once per growing season at 100, 150, 175 or 200 g a.i./ha, timed from between 20% to 50% flowering. Trials compared application rates, application volumes (high and low volumes, ground versus aerial applications) and the presence or absence of a non-ionic surfactant (Ag-Surf, Induce or Agral 90) added to the Proline treatment at application. Disease pressures in all trials were adequate to assess the product for efficacy.

The claim that Proline 480 SC Foliar Fungicide can be applied to canola (*Brassica napus*) and rapeseed *(Brassica rapa)* for control of Sclerotinia stem rot when applied once at the 20% to 40% bloom stage at 150 g a.i./ha; if there is a history of the disease in the field or for dense crop stands, 175 g a.i./ha is supported. The claim was extended to include Oriental mustard (oilseed types only, *Brassica juncea)*. A second application was not supported due to lack of efficacy data.

The claim that Proline 480 SC Foliar Fungicide can be applied to canola and rapeseed using ground and aerial application equipment is supported based on the minimum carrier volumes for ground of 100 L/ha and aerial at 50 L/ha. This is consistent with the recommendations currently listed on the product label.

7.1.4.4 Chickpeas

Sixteen chickpea trials were conducted between 2001 and 2003 in Saskatchewan and North Dakota. Trials tested Proline 480 SC Foliar Fungicide applied from one to three times per season at rates of 100, 150 or 200 g a.i./ha. Application intervals ranged from between 8 to 21 days, but the majority of the trials received applications on 14-day intervals. Other treatments tested in the studies included Proline applied once or twice (at either 150 or 200 g a.i./ha) in an integrated pest management program that alternated Proline with Quadris, Headline or Bravo (a total seasonal maximum of three applications). These three commercial standard products were also tested alone in consecutive application programs for comparative purposes. The five 2003 trials assessed Proline applied three times at 150 g a.i./ha, either with or without an adjuvant (Ag-Surf or Induce). Percentages of disease incidence and severity were assessed for the whole plant, or separately on the leaf, stem and/or pods for all trials.

The claim that Proline 480 SC Foliar Fungicide will control Ascochyta blight on chickpeas when applied up to three times per season at rates of either 150 or 200 g a.i./ha, on 14-day intervals, is supported. Apply at first sign of disease, and apply the higher rate when conditions favour disease development or when growing less disease resistant varieties. Apply by ground application equipment only.

7.1.4.5 Lentils

Five lentil trials were conducted in Saskatchewan in 2002 and 2003. Two varieties were tested, CDC Sovereign and Crimson. Trials compared a single application made at 100, 150 or 200 g a.i./ha, or two applications at 150 or 200 g a.i./ha (same rate for each application). Most applications of Proline included the addition of the adjuvant Ag-Surf, but two trials directly compared Proline with or without the adjuvant. Proline was assessed for efficacy when applied early (early to mid July) or two weeks later (mid July to early August). Disease pressures were, in general, sufficient to assess the product for disease control. Lentil leaf, stem, pod or whole plant were assessed for percentage of disease incidence and disease severity. One trial was excluded from the evaluation as disease pressures were too high before the product was applied, and the product could not be assessed accurately.

The claim that Proline applied at 150 g a.i./ha (315 mL product/ha) at the first sign of disease is supported. A second application may be made 14 days later if conditions remain favourable for continued or increased disease development. A third application was not supported because of lack of efficacy and crop tolerance data.

7.1.5 Total Spray Volume

Proposed minimum carrier volumes for Proline 480 SC were 100 L water/ha (ground application equipment) and 50 L/ha (aerial application). Trials tested the following: wheat at 55–330 L/ha, barley at 110–225 L/ha, canola at 46 (aerial) and 168 (ground) L/ha, chickpeas at 110–200 L/ ha (ground) and lentils at 168–200 L/ha.

7.1.6 Adjuvant

All trials conducted on wheat and barley tested Proline applied with a non-ionic adjuvant. Given that no data were available to compare the efficacy of Proline with and without the adjuvant, it is unknown if the adjuvant increased the efficacy of the product or if the adjuvant had no effect.

For the non-cereal crops, most data did not demonstrate any consistent increase in efficacy when Proline was applied with the adjuvant; however, no decrease in efficacy was noted either. Therefore, it cannot be demonstrated that for optimal disease control, the lowest rate of a spray surfactant must be tank mixed with Proline 480 SC Foliar Fungicide. The proposed label statement regarding adjuvants must be replaced with "The lowest rate of a spray surfactant may be tank mixed with Proline 480 SC Foliar Fungicide."

7.2 Phytotoxicity to Target Plants or Target Plant Products

When Proline 480 SC Foliar Fungicide was applied on wheat, barley, canola, rapeseed, chickpeas and lentils according to the rates and number of applications indicated in the directions for use section of the label, no phytotoxic symptoms were reported. Based on all of the data provided, it is believed that Proline 480 SC Foliar Fungicide is not phytotoxic to plants in general.

7.3 Sustainability

7.3.1 Survey of Alternatives

7.3.1.1 Non-Chemical Control Practices

Non-chemical disease control means include good crop rotation practices, using certified clean seed to prevent seed-borne diseases from developing (such as Ascochyta blight), choosing disease-resistant plant varieties and preventing pathogens from entering fields via mechanical transfer from humans or field equipment. Cleaning up and removing diseased plant material from the previous growing season, which can be a source of inoculum for the current year's disease outbreak, is also provide non-chemical control of diseases. Cultural and sanitation practices can prevent the introduction or development of pathogens in a field, thus reducing the need for curative action.

7.3.1.2 Chemical Control Practices

Table 7.3.1 Alternative Active Ingredients Registered for Control of the Foliar Diseases Listed on the Proline 480 SC Label

Crop	Disease	FRAC Group	Active Ingredient[1]
Wheat	Fusarium head blight (scab)	3 M[5]	Tebuconazole Chlorothalonil
	Septoria glume blotch	3 M[5]	Propiconazole Chlorothalonil
	Septoria leaf blotch	3 11 11 M[3] M[5]	Propiconazole Trifloxystrobin Pyraclostrobin Mancozeb Chlorothalonil
	Tan spot	3 11 11 M[3] M[5]	Propiconazole Trifloxystrobin Pyraclostrobin Mancozeb Chlorothalonil
	Leaf rust	3 11 11 M[3]	Propiconazole Trifloxystrobin Pyraclostrobin Mancozeb
Barley	Fusarium head blight (scab)	—	N/A
	Net blotch	311	Propiconazole Pyraclostrobin
	Scald	311	Propiconazole Pyraclostrobin
	Spot blotch	311	Propiconazole Pyraclostrobin
Canola	Sclerotinia stem rot	22711	Iprodione Vinclozolin Boscalid Azoxystrobin
Chickpeas, lentils	Ascochyta blight	7 11 M[3] M[5]	Boscalid Pyraclostrobin Mancozeb Chlorothalonil

[1] Active ingredients registered as seed treatments are not included.

7.3.2 Compatibility With Current Management Practices Including Integrated Pest Management

Proline 480 SC Foliar Fungicide can be easily introduced into current management practices without the need for new application equipment or materials. Proline 480 SC can be integrated into existing chemical fungicide application schedules as an alternative mode of action for control or suppression of many foliar diseases.

7.3.3 Contribution to Risk Reduction

Prothioconazole, a Group 3 Fungicide, would be a new chemical mode of action for use in controlling foliar diseases on canola, chickpea and lentils. This new fungicide, with a different mode of action, allows for greater alternation of fungicides, which is part of a successful integrated pest management program, and helps in reducing resistance development in fungal populations.

Proline 480 SC Foliar Fungicide has demonstrated no phytotoxic effects on the target plants listed in the directions for use on the product label.

Suppressing fusarium head blight with Proline 480 SC Foliar Fungicide will also decrease the DON level in wheat and barley, thereby reducing the level of mycotoxin in the grain. This is a direct benefit in the quality of grain destined for animal and human consumption.

7.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

According to FRAC, resistance to SBI fungicides usually only occurs after several years of intensive, consecutive use. There is no history of resistance recorded for this active ingredient because prothioconazole is new in North America.

In 2005, the European SBI Working Group within FRAC reported the effectiveness of DMIs and amine fungicides to be stable, in general. For prothioconazole specifically, the Working Group presented the following.

- No shift in sensitivity was reported for powdery mildew (*Blumeria graminis* f. sp. *tritici*) on wheat over the past 10 years.
- Stable populations were reported for wheat eyespot (*Tapesia* spp. [Syn] *Oculimacula* spp.) over the past two years.

7.4 Conclusions

Prothioconazole and the associated end-use product Proline 480 SC Foliar Fungicide have been demonstrated to be effective in suppressing or controlling specific foliar diseases on wheat, barley, canola, rapeseed, Oriental mustard (oil-seed type), chickpea and lentils. Proline 480 SC Foliar Fungicide has been demonstrated to be non-phytotoxic to the listed plants when applied according to the approved label directions.

7.4.1 Summary

Table 7.4.1 Summary of Label Proposals and Recommendations on Cereal Crops

Proposed Label Claim			Supported Use Claims
Crop	**Pest / Number of Applications**	**Rate (g a.i./ha)**	
Wheat	Suppression of fusarium head blight	150–200	Supported as proposed
	Control of Septoria glume blotch	150–200	Supported as proposed
	Control of Septoria leaf blotch	150	Supported as proposed
	Control of tan spot	150	Supported as proposed
	Control of leaf rust	150	Supported as proposed
	A maximum of 2 applications per year (one for fusarium head blight, one for other diseases) with an application interval of 7 to 14 days		Supported as proposed
Barley	Suppression of fusarium head blight	150–200	Supported as proposed
	Control of net blotch	100–150	Supported as proposed
	Control of scald	100–150	Supported as proposed
	Control of spot blotch	100–150	Supported as proposed
	A maximum of 2 applications per year (one for fusarium head blight, one for other diseases) with an application interval of 7 to 14 days		Supported as proposed

Table 7.4.2 Summary of Label Proposals and Recommendations on Non-Cereal Crops

Proposed Use Claims	Accepted Use Claims
Crops: Oilseed Crop Subgroup **Disease:** Control of Sclerotinia stem rot (*Sclerotinia sclerotium*) **Rate:** 150–200 g a.i./ha **Maximum applications per year:** 2 **Application Interval:** Apply between the 20% and 50% bloom stage **PHI:** 36 days	**Crops:** Canola (*Brassica napus*), rapeseed (*Brassica rapa*) and Oriental mustard—oilseed type only (*Brassia juncea*) **Disease:** Control of Sclerotinia stem rot (*Sclerotinia sclerotium*) **Rate:** 150–175 g a.i./ha **Maximum applications per year:** 1 **Application Interval:** Apply between the 20% to 40% bloom stage **PHI:** 36 days
Crops: Chickpeas **Disease:** Control of Ascochyta blight (*Ascochyta* spp.) **Rate:** 150–200 g a.i./ha **Maximum applications per year:** 3 **Application Interval:** 10–14 days **PHI:** 7 days until cutting or swathing of the crop.	Supported as proposed with the following changes: **Disease:** Control of Ascochyta blight (*Ascochyta rabiei*)
Crops: Lentils **Disease:** Control of Ascochyta blight (*Ascochyta* spp.) **Rate:** 150–200 g a.i./ha **Maximum applications per year:** 3 **Application Interval:** 10–14 days **PHI:** 7 days	**Crops:** Lentils **Disease:** Control of Ascochyta blight (*Ascochyta rabiei, Ascochyta fabae* f. sp. *lentis)* **Rate:** 150–200 g a.i./ha **Maximum applications per year:** 2 **Application Interval:** 10–14 days **PHI:** 7 days
Adjuvant: To optimize disease control, the lowest rate of a spray surfactant must be tank mixed with Proline 480 SC Foliar Fungicide.	**Adjuvant:** The lowest rate of a spray surfactant may be tank mixed with Proline 480 SC Foliar Fungicide.

8.0 Toxic Substances Management Policy

During the review of Prothioconazole Technical Fungicide and Proline 480 SC Foliar Fungicide, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track 1 criteria for the following reasons.

- Prothioconazole is not bioaccumulative. The bioconcentration factor in whole fish tissue is 43.9–57.8 for total residues and 19.7 for prothioconazole residues only. Both bioconcentration factor values are below the TSMP Track 1 cut-off criterion of ≥ 5000. Prothioconazole-desthio and prothioconazole-*S*-methyl both have bioconcentration factors below the TSMP Track 1 cut-off criterion (prothioconazole-desthio: whole fish bioconcentration factor of 71.6–94.3 for total residues; prothioconazole-*S*-methyl: estimated bioconcentration factor of 75 based on modelling).

- Total toxic residues (prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl) meet the criteria for persistence because their half-lives in soil (based half-lives in field dissipation studies of up to 296.3 days) and in sediment (based on half-life in anaerobic aquatic systems of 1386 days), exceed the TSMP Track 1 cut-off criteria for soil (≥ 182 days) and sediment (≥ 365 days). The TSMP Track 1 cut-off criteria for water (≥ 182 days) is not met, as the total toxic residue half-life in water, based on aerobic aquatic systems half-life, was 26.8–41.5 days. The vapour pressure and Henry's law constant indicate that prothioconazole will not volatilize from water or moist soil under field conditions; thus, long-range atmospheric transport of prothioconazole is not likely to occur. No half-lives were available for prothioconazole-thiazocine and 1,2,4-triazole in any media.

- The toxicity of prothioconazole, prothioconazole-desthio and prothioconazole-*S*-methyl is discussed in sections 3.6, 4.7 and 6.4.

- Prothioconazole does not form any other major transformation products that meet the TSMP Track 1 criteria. Bioconcentration factors are not available for prothioconazole-thiazocine and 1,2,4-triazole, but they are not expected to bioconcentrate in biological tissues.

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1 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics.

2 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3758; e-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca.

- Prothioconazole (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials, nor are they expected to be generated during the manufacturing process.

- The formulated product does not contain any formulants known to contain TSMP Track 1 substances.

9.0 Regulatory Decision

Prothioconazole and the end-use product Proline 480 SC Foliar Fungicide have been granted temporary registrations for use on wheat, barley, canola, rapeseed, oriental mustard, chickpeas and lentils, pursuant to the Pest Control Products Regulations, subject to submission of the following conditions:

- additional data to address deficiencies in the developmental neurotoxicity study;
- a poultry feeding study;
- validation of the animal analytical method for poultry commodities;
- confirmatory storage stability data of prothioconazole and prothioconazole-desthio in plant commodities; and
- confirmatory storage stability data of prothioconazole, prothioconazole-desthio and prothioconazole-4-hydroxy in fat samples.

List of Abbreviations

µg	microgram
λ	wave length
A	acre
a.i.	active ingredient
ADI	acceptable daily intake
ALD	approximate lethal dose
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
ASAT	aspartate aminotransferase
atm	atm
BBCH	BASF, Bayer, Ciba-Geigy and Hoechst
bw	body weight
bwg	body-weight gain
BWI	body weight per individual
c	control
CAS	Chemical Abstracts Service
cm	centimetre
DGA	D-galactosamine
DI	dietary intake
DMI	demethylation inhibitor
DON	deoxynivalenol
DT_{50}	dissipation time 50%
DT_{90}	dissipation time 90%
dw	dry weight
EC	emulsifiable concentrate
EC_{25}	effect concentration 25%
EC_{50}	effect concentration 50%
ECOD	7-ethoxyresorufin-O-deethylase
EEC	estimated environmental concentration
EH	epoxide hydrolase
EP	end-use product
EROD	ethoxyresorufin-O-deethylase
ETU	ethylenethiourea
EXAMS	Exposure Analysis Modeling System
F_1	first filial generation
F_2	second filial generation
FAH	foci of altered hepatocytes
FC	food consumption
FOB	functional operational battery
FRAC	Fungicide Resistance Action Committee
fw	fresh weight
g	gram
GD	gestation day

GGT	gammaglutamyl transferase
GLP	good laboratory practice
GST	glutatione S-transferase
GUS	groundwater ubiquity score
ha	hectare
HAFT	highest average field trial
Hb	hemoglobin
Hct	hematocrit
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HPLC	high performance liquid chromatography
HPTLC	high performance thin layer chromatography
ICR	impaired cytokine response
IgM	immunoglobulin M
ind	individual
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre
lb	pound
LC_{50}	lethal concentration 50%
LC-MS/MS	high performance liquid chromatography (with electrospray ionization) and tandem mass spectrometry
LD	lactation day
LD_{50}	lethal dose 50%
LEACHM	Leaching Estimation and Chemistry Model
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
m	metre
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mg	milligram
mL	millilitre
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
MSPD	matrix solid phase dispersion
MTDB	maximum theoretical dietary burden
N/A	not applicable
NC	no concentration
n	number of trials
nm	nanometre
NMR	nuclear magnetic resonance
NNM	*N*-nitrosomorpholine
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level

NOER	no observed effect rate
P	parental generation
Pa	Pascal
PBI	plantback interval
PFC	plaque-forming cell
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PND	postnatal day
ppb	parts per billion
PLT	platelet
PMRA	Pest Management Regulatory Agency
PRZM	Pesticide Root Zone Model
PTU	propylthiouracil
R/F	residue-to-feed ratio
REI	re-entry interval
ROLD	repeat oral low dose
RQ	risk quotient
SBI	sterol bio-synthesis inhibitor
SC	soluble concentrate
SD	standard deviation
SOHD	single oral high dose
SOLD	single oral low dose
SPE	solid phase extraction
std. dev.	standard deviation
STMdR	supervised trial median residue
STMR	supervised trial mean residue
t	treated
T3	tri-iodothyronine
T4	thyroxine
THPA	triazolylhydroxypropionic acid
TPO	thyroid peroxidate
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UDPGT	uridine 5'-diphosphatase-glucuronyl transferase
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v	volume
w	weight
WC	water consumption

Appendix I Toxicology

Table 1 Toxicology Summary Table—Prothioconazole

METABOLISM—PROTHIOCONAZOLE			
Rate and extent of absorption and excretion: Male single oral low dose (SOLD 2–5 mg/kg bw), 90–94% absorbed. SOLD males/females 10–16% in urine, 78–84% in feces (triazole label). Male SOLD 5% in urine, 81% in feces (phenyl label). Bile males 90% in bile 24–48 hours (triazole), 93% in bile 24–48 hours (phenyl). Single oral high dose (SOHD 150 mg/kg bw/day) males/females 4–12% in urine, 88–96% in feces (triazole label). Males, peak body concentration (whole body radiography) at 1 hour, then rapidly declined to sacrifice at 168 hours. Females peak at 8 hours. Both sexes peak plasma concentration within 1 hour. Less than 6% radioactivity remaining after 168 hours (SOLD), less than 4% after 48 hours repeat oral low dose (ROLD 2 mg/kg bw/day). Distribution / target organ(s): Highest concentration (relative to organ weight, not administered dose) in liver, followed by kidney, brown/perirenal fat, thyroid and adrenal gland. Metabolites: Eighteen metabolites plus parent found in excreta. Reaction types were desulfuration, oxidative hydroxylation of the phenyl moiety and glucuronic acid conjugation. In feces, parent was most common, then prothioconazole-desthio. All others were < 8% of administered dose. 1,2,4-triazole metabolite was not found in the feces. For urine, major metabolite was prothioconazole-*S*- or -*O*-glucuronide, preferentially excreted in females. 1,2,4-triazole was found 0.8–2.3% of administered SOLD/SOHD.			
STUDY	**SPECIES, STRAIN AND DOSES**	**NOAEL and LOAEL mg/kg bw/day**	**TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS**
Acute Studies—Prothioconazole			
Oral	99.8% a.i. 3 SPF-bred Wistar rats/sex, 5000 mg/kg, Cremophor EL 2% vehicle Toxic class method	$LD_{50} \geq 6200$ mg/kg	No mortality Diarrhea ↓ motility
Dermal	98.8% a.i. 5 SPF-bred Wistar rats/sex, 2000 mg/kg, water vehicle	$LD_{50} > 2000$ mg/kg	No mortality Slight body-weight loss in females, especially week 1 Reddening and scale formation at test site
Inhalation	98.8% a.i. 5 SPF-bred Wistar rats/sex/dose at 0 or 4.99 mg/L, PEG400-ethanol vehicle	$LC_{50} > 4.99$ mg/L	No mortality ↓ bwg day 3 Piloerection, ungroomed coat, bradypnea, laboured breathing, nasal discharge, red encrustations on muzzle/nostrils, reduced motility ↓ body temperature
Eye Irritation	98.8% a.i. 3 male Himalayan rabbits, 100 mg, washed at 24 hours	MIS 0.67/110 at 1 hour MAS 0.22/110 at 24, 48 and 72 hours	Minimally irritating

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Skin Irritation	98.8% a.i. 3 male Himalayan rabbits, 500 mg including moisture, 4 hours, water vehicle	No irritation	Non-irritating
Skin Sensitization (Magnusson and Kligman)	98.8% a.i. 10 male Hsd Poc:DH guinea pigs (2 × 5 control) 5% injection induction 25% patch induction 12% patch challenge	One slight response in 1/10 animals	Not a sensitizer
Acute Studies—Prothioconazole Asymmetric Isomer			
Oral	98.7% a.i. 3 SPF-bred Wistar rats/sex, 2000 mg/kg, Cremophor EL 2% vehicle Toxic class method	LD_{50} > 2000 mg/kg	No mortality
Acute Studies—Prothioconazole Methyl			
Oral	98.3% a.i. 3 SPF-bred Wistar rats/sex, 2000 mg/kg, Cremophor EL 2% vehicle Toxic class method	LD_{50} > 2000 mg/kg	No mortality
Acute Studies—Prothioconazole Asymmetric Disulfide			
Oral	95.3% a.i. 3 SPF-bred Wistar rats/sex, 2000 mg/kg, Cremophor EL 2% vehicle Toxic class method	LD_{50} > 2000 mg/kg	No mortality
Acute Studies—Prothioconazole Sulfonic Acid Potassium Salt			
Oral	99.1% a.i. 3 SPF-bred Wistar rats/sex, 200 mg/kg, demineralized water vehicle 3 female SPF-bred Wistar rats, 2000 mg/kg Toxic class method	LD_{50} > 200 mg/kg males, > 300 < 500 mg/kg females	**200 mg/kg** No mortality **2000 mg/kg** 3/3 females dead, uncoordinated/spastic gait, laboured breathing, narrowed palpebral fissures, ↓ motility and reactivity, slightly collapsed lungs, glandular stomach with dark red discolourations and pale liver discolourations

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Acute Studies—Prothioconazole Alpha Hydroxy Desthio			
Oral	98.5% a.i. 3 SPF-bred Wistar rats/sex, 2000 mg/kg, Cremophor EL 2% vehicle Toxic class method	LD_{50} > 2000 mg/kg	No mortality, piloerection, ↓ motility and reactivity, uncoordinated gait, laboured breathing and narrowed palpebral fissures in males
Acute Studies—Prothioconazole Alpha Acetoxy Desthio			
Oral	99.3% a.i. 3 SPF-bred Wistar rats/sex, 2000 mg/kg, Cremophor EL 2% vehicle Toxic class method	LD_{50} > 2000 mg/kg	No mortality, piloerection, ↓ motility and reactivity, uncoordinated gait, laboured breathing and narrowed palpebral fissures in males
Acute Studies—Prothioconazole Benzylpropyldiol			
Oral	98.4% a.i. 3 SPF-bred Wistar rats/sex, 2000 mg/kg, aqueous CMC 0.5% vehicle Toxic class method	LD_{50} > 2000 mg/kg	No mortality, salivation in females
Acute Studies—Prothioconazole-triazolinone			
Oral	99.9% a.i. 3 SPF-bred Wistar rats/sex, 2000 mg/kg, Cremophor EL 2% vehicle Toxic class method	LD_{50} > 2000 mg/kg	1 male died, ↓ motility and reactivity, uncoordinated gait and laboured breathing, lateral and/or abdominal position in males, spastic and temporary creeping gait, salivation, narrowed palpebral fissures in females
Acute Studies—Prothioconazole-deschloro			
Oral	96.8% a.i. 6 female SPF-bred Wistar rats, 2000 mg/kg, Cremophor EL 2% vehicle Toxic class method	LD_{50} > 2000 mg/kg	No mortality
Skin Sensitization (Magnusson and Kligman)	96.8% a.i. 20 female Crl:HA guinea pigs (10 control) 2.5% injection induction 50% patch induction 50% patch challenge	Positive response in 10/20 animals	Potential sensitizer

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Acute Studies—Formulation Prothioconazole 480 SC / Proline 480 SC 480 SC			
Oral	40.6% a.i. female Wistar rats, 175, 550, 2000 and 5000 mg/kg Up-down method	LD_{50} > 2000, but < 5000 mg/kg	**175 mg/kg** 0/1 died **550 mg/kg** 0/1 died **2000 mg/kg** 0/3 died **5000 mg/kg** 3/3 died **2000 and 5000 mg/kg** Loose stools, greenish stain in perianal region, ↓ activity, prostrate, laboured respiration, yellow wet urinogenital and perianal area, alopecia, hind quarter laceration
Dermal	40.6% a.i. 5 Wistar rats/sex, 5000 mg/kg	LD_{50} > 5000 mg/kg	No mortality Wetness and yellow stain in urogenital area, red stain on the nose, red lesion on abdomen, thinning hair at the right front paw
Inhalation	40.6% a.i. 5 Wistar rats/sex at 0.852 mg/L	LC_{50} > 0.852 mg/L	No mortality Piloerection, laboured breathing, hypothermia, decreased body weights compared to controls Slightly acutely toxic
Eye Irritation	40.6% a.i. 3 New Zealand white rabbits, 0.1 mL, unwashed	No irritation	Non-irritating
Skin Irritation	40.6% a.i. 3 New Zealand white rabbits, 0.5 mL, 4 hours	MIS 0.67/8, 1 hour MAS 0.2/8, 24–72 hours	Slightly irritating
Skin Sensitization (maximization)	40.6% a.i. 20 guinea pigs (10 control) 5% injection induction 100% patch induction 50% patch challenge	No response	Not a sensitizer
Short-Term Toxicity—Prothioconazole			
28-day, dermal	10 HsdCpb:WU rats/sex/dose, 0, 100, 300 or 1000 mg/kg bw/day, 6 hours/day, 5 days/week	NOAEL 1000 mg/kg bw/day LOAEL not determined	**1000 mg/kg bw/day** No effects

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
28-day, dietary Range finding	5 Wistar rats/sex/dose, 0, 400, 2000, 10 000 ppm (0, 18.6/18.8, 145.7/151.0, 951.7/1032.5 mg/kg bw/day), diet contained 1% peanut oil	No NOAEL or LOAEL set for range finding studies	**≥ 18.6/18.8 mg/kg bw/day** ↓ ALD in males ↑ EH in males **≥ 145.7/151.0 mg/kg bw/day** ↑ ALP ↑ GST, UDPGT **951.7/1032.5 mg/kg bw/day** ↓ bw in males ↓ bwg ↓ food consumption in males ↑ water consumption ↑ basophilic tubules ↑ tubule dilation ↓ urine volume ↑ urea ↑ ALT ↓ EROD ↑ ECOD in males ↓ ALD in females ↑ cholesterol ↑ absolute and relative liver weight in females ↓ T4 in females (↓ 41%) ↑ TSH in females (↑ 114%) Pale, discoloured, marbled kidneys in males

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
28-day, oral Supplemental, to assess dosing method	5 Wistar rats/sex/dose, 0, 10 000 ppm in neat or silica stabilized in diet, 1000 mg/kg bw/day gavage (diet is equivalent to 1078/850 mg/kg bw/day for stabilized and 1038/1067 neat), diet contained 1% peanut oil	N/A Plasma concentrations **Neat diet** 25.0–49.6 nmol/mL **Silica stabilized** 11.0–19.6 nmol/mL **Gavage** 66.3–108.3 nmol/mL	**Neat diet** Piloerection ↓ bw, bwg ↑ water consumption ↑ absolute and relative liver weight with histopath in females Cytoplasmic change in liver in females ↑ basophilic tubules ↑ ECOD in males ↑ ALD in males ↑ EH ↑ GST **Silica stabilized** ↓ bwg in females ↑ food consumption ↑ absolute liver weight males Cytoplasmic change in liver males ↑ basophilic tubules in females ↑ ECOD in males ↑ EH ↑ GST in males, UDPGT in males **Gavage** ↓ bwg males ↑ absolute and relative liver weight with clinical chemistry in females Cytoplasmic change in liver ↓ absolute and relative kidney weight with basophilic tubules in males ↑ ECOD in males ↑ EH ↑ GST, UDPGT Highest plasma levels of both parent and desthio of all groups

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
14-week, gavage	10 CD-1 mice/sex/dose, 0, 25, 100, 400 mg/kg bw/day, 0.5% Tylose	NOAEL 25 mg/kg bw/day LOAEL 100 mg/kg bw/day	**≥ 100 mg/kg bw/day** ↑ cholesterol in females ↑ liver weight ↑ incidence hepatocyte hypertrophy and cytoplasmic change ↑ P450 ↑ ECOD, EROD, ALD ↑ GST in females **400 mg/kg bw/day** ↑ ASAT in males ↓ albumin in males ↑ cholesterol in females ↑ UDPGT in females ↑ incidence liver lobulation in males ↑ conjugation liver enzymes ↑ vacuolation and focal necrosis in liver in males ↑ periportal fatty change and vacuolation in females

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
14-week, gavage	10 Wistar rats/sex/dose, 0, 20, 100, 500 mg/kg bw/day), also 5 week recovery groups 10/sex/dose, 0, 500 mg/kg bw/day), also 4 week immuno-toxicological, 0, 20, 100, 500 mg/kg bw/day, 0.5% Tylose Immunotox effects combined with regular dosing group for purposes of notes in right-hand column Terminal body weight and food consumption for control animals: bw = 380 g FC = 20.9 g/day	NOAEL 100 mg/kg bw/day LOAEL 500 mg/kg bw/day Not considered immunotoxic, but based on non-GLP investigation	**≥ 20 mg/kg bw/day** ↓ aldrin epoxidase in males **≥ 100 mg/kg bw/day** ↑ incidence single cell necrosis in liver in males **500 mg/kg bw/day, 14-week sacrifice** One female euthanized with tongue inflammation, basophilic tubules in kidney and dilated urinary bladder ↑ water consumption ↑ cholesterol ↓ triglyceride males ↑ epoxide hydrolase ↑ 7-ethoxycoumarin deethylase males ↓ 7-ethoxycoumarin deethylase in females ↑ UDP-glucuronyltransferase males ↓ α, ↑ β Testosterone hydroxylation males/females ↓ urine volume ↑ urine protein ↑ absolute and relative liver weight in females ↓ absolute and relative spleen weight in males ↑ incidence hepatocellular hypertrophy and cytoplasmic change ↑ liver congestion in males ↑ severity of basophilic tubules of renal cortex in males **500 mg/kg bw/day, recovery** ↓ cholesterol ↓ triglyceride in females ↓ urine volume ↓ urine protein in males

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day dog, gavage	48 Beagle dogs (4/sex/dose) (0.5% methyl cellulose with 0.4% Tween 80 in deionized water) 5 days/week 0, 25, 100 or 300 mg/kg bw/day) with a recovery group dosed at 300 mg/kg bw/day (8-week recovery period).	NOAEL 25 mg/kg bw/day LOAEL 100 mg/kg bw/day	≥ **100 mg/kg bw/day** ↑ ALT, ALP, GGT ↑ multifocal chronic interstitial fibrosis with associated tubular regeneration and minimal inflammatory cell infiltrate in kidneys (not completely reversible, though reversibility only checked at 300 mg/kg bw/day) **300 mg/kg bw/day** ↓ bwg (main males ↓ 37%, recovery in males ↓ 19%, recovery in females ↓ 16%) ↓ T4, TSH ↑ proximal tubular degeneration, kidneys in males ↑ relative liver, kidney and thymus weights in females Cysts on kidney surface
12-month, gavage	4 beagle dogs/sex/dose, (0.5% methyl cellulose with 0.4% Tween 80 in deionized water) 0, 5, 40, 125 mg/kg bw/day	NOAEL 5 mg/kg bw/day LOAEL 40 mg/kg bw/day	≥ **5 mg/kg bw/day** ↑ ALP in females ↑ P450 in females ↓ ALT in males ↓ urine calcium ↑ absolute and relative spleen weight in females ≥ **40 mg/kg bw/day** ↑ ALP in males ↓ T3, T4 ↑ *O*-demethylase in males Chronic inflammation and pigmentation of the kidney in males Crystals in the kidney in females Spleen pigmentation in females **125 mg/kg bw/day** ↓ bwg in males ↓ bw (↓ 21%), bwg (↓ 42%), food consumption (↓ 47%) in females, ↓ bw (↓ 14%) in males ↑ absolute and relative liver weights ↑ relative kidney weights in females Extramedullary hematopoiesis in females ↑ urine volume ↑ blood levels in urine in males Crystals and mineralization of the kidney in males Chronic inflammation and fibrosis of the kidney in females ↑ liver pigmentation Fibrosiderotic plaques in the spleen in females

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Short-Term Toxicity—Prothioconazole-Sulfonic Acid Potassium Salt			
13-week, dietary Prothioconazole-sulfonic acid potassium salt	10 Wistar rats/sex/dose, 0, 30, 125, 500, 2000 ppm (0, 2.1/2.6, 8.7/9.7, 34.3/40.4, 135.9/163.0 mg/kg bw/day), diet contained 1% peanut oil	NOAEL 34.3 mg/kg bw/day LOAEL 135.9 mg/kg bw/day	**135.9/163.0 mg/kg bw/day** One moribund sacrifice in females, few dark red areas of the cerebrum and spotted kidneys Transitional cell hyperplasia in urinary bladder in males, one with grade 3 hyperplasia and incipient papillary growth pattern ↑ incidence and severity of ovarian cysts ↓ corpora lutea Focal degeneration of germinal epithelium in testes (1, 0, 0, 0, 3) with no related testicular findings ↑ vaginal proestrus
Chronic Toxicity and Oncogenicity—Prothioconazole			
53-week rat, gavage with FOB	20 Wistar rats/sex/dose, (aqueous solution of 0.5% Tylose) 0, 5, 50, 750 mg/kg bw/d FOB weeks 27 and 52 with 10 rats/dose	NOAEL 50 mg/kg bw/day LOAEL 750 mg/kg bw/day FOBs were negative	**750 mg/kg bw/day** ↓ bw (↓ 8–15% in males, ↓ 7–14% in females), bwg (↓ 21% in males, ↓ 23% in females) ↑ salivation ↑ water consumption ↑ urine excretion ↓ hemoglobin ↑ thrombocyte and leukocyte counts ↓ T4 ↑ ALP, bilirubin, cholesterol, triglycerides ↓ plasma glucose, protein ↑ liver weight with granular appearance of the hepatocellular cytoplasm ↑ plasma urea and creatinine ↓ urine pH Yellow brown crystalloids in urine sediment ↑ relative kidney weight Roughened kidney surface ↑ severity of chronic progressive nephropathy ↑ incidence of simple urothelial hyperplasia in the bladder with minimal focal inflammatory infiltration

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
2-year rat, gavage Limited study (high mortality at study end—meets USEPA requirements with 50% survival at 18 months and 25% survival at 24 months, necropsy possible on all animals (including intercurrent deaths)	50 Wistar Hsd Cpb:WU rats/sex/dose (aqueous solution of 0.5% Tylose) 0, 5, 50 or 750/500/625 mg/kg bw/day (the high dose was reduced from 750 mg/kg bw/day to 500 mg/kg bw/day for males at study week 84, and to 625 mg/kg bw/day for females at study week 56)	NOAEL 50 mg/kg bw/day for both sexes LOAEL 500 mg/kg bw/day No evidence of carcinogenicity	**50 mg/kg bw/day** ↑ hypertrophy/cytoplasmic change in liver in males ↑ urine excretion ↑ platelets, week 104, males (↑20%) **750/500/625 mg/kg bw/day** ↑ mortality (38, 36, 34 and 74% in males and 46, 36, 30 and 46% in females at study end) ↑ emaciation, poor general condition and urine excretion prior to dose reduction. ↓ bw (20% in males, 12% in females)/ bwg (29% in males, 20% in females) ↑ FC and WC ↑ neutrophils, thrombocytes in males, leukocytes, monocytes in males, lymphocytes in females ↓ erythrocytes in males, Hb in males, Hct in males ↑ ALP, creatinine in males, urea in males ↑ urine volume ↓ urine pH in males ↓ urine protein, first 18 months, then increased in males Yellow brown crystalloids in urine sediment ↑ liver and kidney weights ↑ hypertrophy and eosinophilic/clear cell focus in liver ↑ chronic progressive nephropathy in kidney ↑ transitional cell hyperplasia in urinary bladder ↓ T4

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
80-week mouse, gavage	60 Crl:CD-1 (ICR)BR mice/sex/dose (0.5% Tylose aqueous solution) 0, 10, 70 or 500 mg/kg bw/day	NOAEL 10 mg/kg bw/day LOAEL 70 mg/kg bw/day No evidence of carcinogenicity	≥ **70 mg/kg bw/day** ↓ bwg (↓ 26% in males, ↓ 22% in females) ↑ absolute (12–25% in males) and relative (16–39% in males, 10–39% in females) liver weights ↑ distinct lobulation in liver in males ↑ fluid in body cavity in females (unknown toxicological significance) ↑ centrilobular hypertrophy in males ↑ tubular degeneration/regeneration in kidneys males **500 mg/kg bw/day** ↓ bw (5–10% in males, 4–13% in females), ↓bwg ↓ absolute and relative kidney weights in males ↓ absolute kidney weight in females ↑ absolute liver weight (21% females) ↓ uterus weight, ↓ incidence of consistency change in uterus ↓ absolute ovary weight ↑ discolouration and surface change in kidneys ↑ fluid in body cavity in males (unknown toxicological significance) ↓ discolouration of seminal vesicles and ↑ inflammation in seminal vesicles in males (unknown toxicological significance) ↑ centrilobular hypertrophy in females ↑ tubular degeneration/regeneration in kidneys in females ↑ subcapsular tubular degeneration with interstitial fibrosis in kidney Lobulation of liver in males

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Reproduction and Developmental Toxicity—Prothioconazole			
Multigeneration reproduction, gavage	30 Wistar rats/sex/dose 0, 10, 100, 750 mg/kg bw/day (0.5% methylcellulose and 0.4% Tween 80)	**Parental** NOAEL 100 mg/kg bw/day LOAEL 750 mg/kg bw/day **Offspring** NOAEL 100 mg/kg bw/day LOAEL 750 mg/kg bw/day **Reproductive** NOAEL 100 mg/kg bw/day LOAEL 750 mg/kg bw/day	**≥ 100 mg/kg bw/day** **P adults** ↑ relative seminal vesicle weight (↑ 14–15%) ↓ absolute and relative thymus weight in females (↓ 28, 29% resp.) ↓ bw in males, premating (↓ 6–8%) **750 mg/kg bw/day** **P adults** **Parental** ↓ food efficiency, ↓ bw/bwg, ↑ food consumption in males ↑ absolute liver weight ↑ relative kidney weight in males Multifocal cortical nephrosis in males Hepatocytomegaly in males **Reproductive** ↓ number of estrous cycles ↑ length of estrous cycle ↓ corpora lutea (↓ 42%) ↓ pre-antral follicles (↓ 22%, not statistically significant) **F_1 adults** **Parental** ↓ bw, bwg in males ↑ relative liver weight Hepatocytomegaly ↑ relative kidney weight in males Multifocal cortical nephrosis in males **Reproductive** ↓ number of estrous cycles ↑ relative epididymus, prostate, epicauda, no histopathology (unknown significance) ↑ time to insemination ↓ corpora lutea (↓ 21%, not statistically significant) ↑ pre-antral follicles (↑ 30%) **F_1 pups** ↑ days, preputial separation (not measured in F_2) Pups, both sexes, both generations ↓ bw

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity, gavage	26 female Hsd Cpb:WU SPF Wistar rats/dose (0.5% carboxy methylcellulose suspension in demineralized water) 0, 80, 500, 1000 mg/kg bw/day GD 6–19	**Maternal** NOAEL 80 mg/kg bw/day LOAEL 500 mg/kg bw/day **Developmental** NOAEL 80 mg/kg bw/day LOAEL 500 mg/kg bw/day Teratogenic at maternally toxic doses	**Maternal** **≥ 500 mg/kg bw/day** ↑ urination/water consumption (no histopath performed on kidneys) ↓ bwg (corrected ↓ 21–31%) ↓ T4 **1000 mg/kg bw/day** bw loss days 6-8 ↓ FC ↑ ALT, ALP ↓ triglycerides ↑ absolute and relative liver weight, slight Focal necrosis (0, 1, 1, 2) **Developmental** **≥ 500 mg/kg bw/day** Incomplete or unossified digits, toes; sternebrae, pubic bone Dysplastic pubic bone (0, 0, 1, 1) Left punctiform 14th rib by litter **1000 mg/kg bw/day** Microphathalmia ↓ fetal weights Dilatation of renal pelvis Bilateral punctiform 14th rib
Developmental toxicity, gavage Provided after initial risk assessment	25 female Wistar Hanover rats/dose (0.5% CMC and deionized water) 0, 20, 80 750 mg/kg bw/day GD 6–20	**Maternal** NOAEL 80 mg/kg bw/day LOAEL 750 mg/kg bw/day **Developmental** NOAEL 80 mg/kg bw/day LOAEL 750 mg/kg bw/day	**Maternal** **750 mg/kg bw/day** ↓ bwg and FC ↑ WC **Developmental** **750 mg/kg bw/day** ↑ rudimentary ribs

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity, dermal Supplemental Limit Dose	29–30 female Wistar rats/group (6 hours/day) 1000 mg a.i./kg bw/day (limit dose), as EC 250 formulation (250 mg a.i./kg bw/day), 1:3 diluted EC 250 formulation (62.5 mg a.i./kg bw/day) GD 6–19	**Maternal** NOAEL 1000 mg/kg bw/day (highest dose tested) LOAEL not determined **Developmental** NOAEL 1000 mg/kg bw/day (highest dose tested) LOAEL not determined	**Maternal** ↑ postimplantation loss (compared with concurrent controls), but the mean/animal was only slightly ↑ in consideration of standard deviation **Developmental** ↑ postimplantation loss (compared with concurrent controls), but the mean/animal was only slightly ↑ in consideration of standard deviation
Developmental toxicity, gavage	24 female Chinchilla rabbits/dose 0, 10, 30, 80, 350 mg/kg bw/day 6 and 7 females were added to the 10 and 80 mg/kg bw/day groups respectively due to insufficient pregnancy rate	**Maternal** NOAEL 80 mg/kg bw/day LOAEL 350 mg/kg bw/day **Developmental** NOAEL 80 mg/kg bw/day LOAEL 350 mg/kg bw/day Not teratogenic	**Maternal** **350 mg/kg bw/day** ↑ total resorptions (2, 1, 1, 0, 3) ↑ abortions (excluding resorptions) (0, 0, 0, 0, 3) ↓ food consumption ↓ bwg ↑ postimplantation loss ↓ live fetuses/dam ↓ placenta weight (slight) **Developmental** **350 mg/kg bw/day** ↓ bw ↑ total resorption (2, 1, 1, 0, 3)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Reproduction and Developmental Toxicity—Prothioconazole-deschloro			
Developmental toxicity, gavage Supplemental	8 female Wistar rats/dose (0.5% aqueous carboxy methylcellulose) 0, 40, 200 or 1000 mg/kg bw/day GD 6–19	N/A	**Maternal** **200 mg/kg bw/day** ↓ total number of live fetuses **≥ 200 mg/kg bw/day** ↓ bwg (overall ↓ 13–18%, corrected ↓ 34–37%) **1000 mg/kg bw/day** ↑ urination, WC (varied in time of onset and persistence) White spots on two placentas-same dam (unknown toxicological significance) **Developmental** **1000 mg/kg bw/day** ↑ slight dilation of renal pelvis and dilation of ureter ↑ retarded ossification of skull bones and wavy ribs ↑ 14th ribs and vertebral bodies ↑ macroglossia (2 fetuses/1 dam)
Reproduction and Developmental Toxicity—Prothioconazole Sulfonic Acid Potassium Salt			
Developmental toxicity, gavage	25 female WIST Hanlbm: (SPF) rats/dose (bidistilled water vehicle) 0, 30, 150 or 750 mg/kg bw/day GD 6–20	**Maternal** NOAEL 150 mg/kg bw/day LOAEL 750 mg/kg bw/day **Developmental** NOAEL 150 mg/kg bw/day LOAEL 750 mg/kg bw/day	**Maternal** **750 mg/kg bw/day** ↑ mortalities (6 died pregnant, 1 died non-pregnant) ↓ bwg (↓ 34%), ↓ corrected bwg (-3.5% vs 8.8% in vehicle controls) ↓ FC (↓ 16%) 3 dams with total postimplantation loss (due to high maternal toxicity) **Developmental** **750 mg/kg bw/day** ↓ fetal body weight (4.8, 4.9, 4.9, 4.2 grams)
Developmental toxicity, gavage Supplemental—only a cursory examination was performed	7 female WIST Hanlbm: (SPF) rats/dose (bi-distilled water vehicle) 0, 30, 100, 500 or 1000 mg/kg bw/day GD 6–20	N/A	**Maternal** **1000 mg/kg bw/day** Dams found dead/killed between days 10 and 12 (due to systemic toxicity) Ruffled fur and/or sedation ↓ FC **Developmental** No treatment-related differences

Study	Species and Strain or Cell Type and Concentrations or Doses	Results
Genotoxicity—Prothioconazole and Metabolites		
Gene mutations in bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation) or 1.6–500 µg/plate (pre-incubation); with and without activation	Negative
Gene mutations in bacteria Prothioconazole deschloro	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation) or 5–1581 µg/plate (pre-incubation); with and without activation	Negative
Gene mutations in bacteria Prothioconazole alpha-acetoxy-desthio	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation and pre-incubation); with and without activation	Negative
Gene mutations in bacteria Prothioconazole sulfonic acid potassium salt	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation and pre-incubation); with and without activation	Negative Judged unacceptable due to low background spontaneous revertants in TA 100
Gene mutations in bacteria Prothioconazole benzylpropyldiol	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation) or 4–256 µg/plate (pre-incubation); with and without activation	Negative
Gene mutations in bacteria Prothioconazole methyl	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation) or 16–512 µg/plate (pre-incubation); with and without activation	Negative
Gene mutations in bacteria Prothioconazole asymmetric isomer	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation and pre-incubation); with and without activation	Negative
Gene mutations in bacteria Prothioconazole asymmetric disulfide	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation and pre-incubation); with and without activation	Negative

Study	Species and Strain or Cell Type and Concentrations or Doses	Results
Gene mutations in bacteria Prothioconazole alpha-hydroxy-desthio	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation and pre-incubation); with and without activation	Negative
Gene mutations in bacteria Prothioconazole-triazolinone	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 16–5000 µg/plate (plate incorporation) or 1.6–500 µg/plate (pre-incubation); with and without activation	Negative
Gene mutations in mammalian cells in vitro	Chinese hamster lung V79 cells (HGPRT locus) 25–175 µg/mL, then 5–150 µg/plate -S9 75–200 µg/mL with activation +S9	Negative
Unscheduled DNA synthesis in vivo	Primary rat hepatocytes (male clrSD rats) 2500 or 5000 mg/kg (single oral dose; primary cultures scored for unscheduled DNA synthesis 4 and 16 hours after dose administration)	Negative
Unscheduled DNA synthesis in vitro	Primary rat hepatocytes (male clrSD rats) 1.0–40 µg/mL (first test, 16–24 hours) 0.5–20 µg/mL (second test, 16–24 hours)	Equivocal, but was negative in vivo
Chromosome aberrations in vitro	Chinese hamster lung V79 cells 75–150 µg/mL ± S9 for 18 and 30 hour harvests	Positive, but was considered secondary to cytotoxicity
Chromosome aberrations in vitro Prothioconazole Deschloro	Chinese hamster ovary cells 60–300 µg/mL ± S9 for 18 hours (180–300 for 30 hours also) Additionally, 12–60 µg/mL for 18 hours -S9	Negative
Micronucleus assay in vivo	Male and female Hsd/Win:NMRI mice 250 mg/kg (single intraperitoneal dose; bone marrow harvested 16, 24 and 48 hours postdosing)	Negative
Micronucleus assay in vivo	Male Hsd/Win:NMRI mice 50, 100, 200 mg/kg (two intraperitoneal doses, separated by 24 hours; bone marrow harvested 24 hours postdosing)	Negative

Study	Species and Strain or Cell Type and Concentrations or Doses		Results
Special Studies—Prothioconazole			
Inhibition of liver cytochrome p-450-dependent monooxygenases in liver microsomes Non-guideline	Hepatic microsomes of both mice and rats were dosed in vitro		Unacceptable, no conclusions could be reached due to multiple deficiencies
Interactions with thyroid peroxidase-catalyzed reactions (in vitro) Non-guideline	Hog thyroid microsomes purity of Prothioconazole not specified Reference compounds: ETU, PTU, 3-mercapto-1,2,4-triazole (a basic thiourea moiety of prothioconazole) and JAU 6953 (a related thiourea derivative)	N/A	TPO-catalyzed guaiacol oxidation was inhibited by compounds tested. 3-mercapto-1,2,4-triazole had the lowest IC_{50} value (i.e., lowest concentration required to inhibit the reaction by 50%), then PTU , prothioconazole, JAU 6953. (initial indication that TPO may be irreversibly inhibited) PTU, ETU, prothioconazole, JAU 6953 and 3-mercapto-1,2,4-triazole dose-dependently suppressed TPO-catalyzed iodine formation temporarily. Following suppression, iodine reappeared. The rate was then similar to controls. 3-mercapto-1,2,4-triazole suppressed the rate of the reappearing iodine formation longer than the other compounds.
Plaque forming assay in mice, gavage Report for positive control not provided	8 Crl:CDI(ICR) mice/sex/dose (0.5% aq Tylose) 0, 25, 100, 400 mg/kg	Supplemental, thymus weights, spleen cell viability and IgM PFC activity per spleen were not assessed No evidence of immunosuppression	**25 mg/kg bw/day** ↓ Spleen cell counts in males **400 mg/kg bw/day** Piloerection in males ↑ plaque-forming cells in males (↑125%)—study authors attribute to stress

Study	Species and Strain or Cell Type and Concentrations or Doses		Results
Determination of enzyme activities and concentration of parent in the liver and kidneys of dogs in the subchronic gavage study Non-guideline	4 beagle dogs/sex/dose, 0, 25, 100, 300 mg/kg bw/day gavage for 13 weeks. Recovery groups 0, 300 mg/kg bw/day for 13 weeks plus 4 week recovery	Supplemental follow-up to a previous subchronic study	No phase I or phase II enzyme activity changes in males, only epoxide hydrolase in liver increased in females at 100 and 300 mg/kg bw/day, reversible after recovery In males, epoxide hydrolase in kidneys was reduced at 300 mg/kg bw/day, but this was reversible too In the liver, the tissue concentration of parent to desthio was 10:1 In the kidney, prothioconazole-desthio was undetectable Overall, tissue concentrations were about 3× higher in females vs males
Acute neurotoxicity, gavage	12 Wistar (Crl:Wl(HAN)BR rats/sex (0.5% methylcellulose/ 0.4% Tween 80) 0 (vehicle), 200, 750 or 2000 mg/kg bw	NOAEL 200/750 mg/kg bw/day (males/females) LOAEL 750/2000 mg/kg bw/day (males/females)	≥ **750 mg/kg bw/day** ↓ motor (↓ 29–32% in males) and locomotor (↓ 33–39%) activity on day 0 ↑ brown perianal stain days 1–5 (3/12, 7/12, 11/12, 12/12 in males, 0/12, 0/12, 8/12, 11/12 in females) (not adverse alone) **2000 mg/kg bw/day** ↓ motor (↓ 45% females) and locomotor (↓ 43% females) activity on day 0
Subchronic neurotoxicity, gavage	12 Wistar (Crl:WI(HAN)BR) rats/sex/group, 5 days/week (0.5% methylcellulose/ 0.4% Tween 80 in deionized water) 0, 100, 500 or 1000 mg/kg bw/day (analytically determined 0, 98, 505 and 1030 mg/kg bw/day)	NOAEL 500 mg/kg bw/day LOAEL 1000 mg/kg bw/day	≥ **500 mg/kg bw/day** ↑ urine stain (0/12,0/12, 8/12, 12/12 in males and 0/12,0/12, 9/10, 11/11 in females) (not adverse alone) **1000 mg/kg bw/day** ↑ oral stain (0/12,0/12, 0/12, 3/12 in males, 0/12,0/12, 0/10, 1/11 in females) ↓ total bwg (↓ 24% males) ↓ final bw (↓ 8% females)

Study	Species and Strain or Cell Type and Concentrations or Doses	Results
Compound-Induced Mortality Two-year rat study at 500 mg/kg bw/day		
Recommended ARfD There are no acute effects of concern for the general population. The only potential concern is the uncertainty around the developmental neurotoxicity study regarding altered brain morphometrics and peripheral nerve degeneration due to a lack of measurements at low and mid doses. Consequently, it is appropriate to set a reference dose for females 13+. Females 13+: 0.002 mg/kg bw/day based on a rabbit developmental study with prothioconazole-desthio. The NOAEL of 2 mg/kg bw/day with the standard uncertainty factor of 100-fold was applied to account for intraspecies and interspecies variability, and an additional 10-fold safety factor for severity of endpoint in the fetus as the malformations (arthrogryposis) occurred at maternally non-toxic doses.		
Recommended ADI General population: 0.004 mg/kg bw/day based on the two year oncogenicity study in rats with prothioconazole-desthio. The NOAEL was 1.1 mg/kg bw/day, based on liver toxicity. The standard uncertainty factor of 100-fold was applied to account for intraspecies and interspecies variability, and an additional 3-fold safety factor was recommended to protect for sensitivity of the young in the prothioconazole-desthio developmental neurotoxicity study (malocclusion and deviated snout). This provides margins of safety (MOS) of 900 to the NOEL for progressive malocclusion and deviated snout in the desthio developmental neurotoxicity study and for the lack of morphometric measurements at the lowest dose tested in the developmental neurotoxicity study. Females 13+: 0.002 mg/kg bw/day based on a rabbit developmental study with prothioconazole-desthio. The NOAEL was 2 mg/kg bw/day, based on fetal malformations. The standard uncertainty factor of 100-fold was applied to account for intraspecies and interspecies variability, and an additional 10-fold safety factor was recommended to protect for severity of endpoint in the fetus as the malformations (arthrogryposis) occurred at maternally non-toxic doses. This provides an MOS of 1800 to the NOEL for progressive malocclusion and deviated snout and for the lack of morphometric measurements at the lowest dose tested in the developmental neurotoxicity study.		
Toxicological Endpoints for Occupational Risk Assessment – Dermal, short and intermediate, 30 mg/kg bw/day (prothioconazole-desthio rat dermal developmental) with 300 MOE (standard 100-fold for intraspecies and interspecies differences and an additional 3-fold to account for severity of effects in the young [variations at maternally non-toxic doses]). – Inhalation, short and intermediate, 2 mg/kg bw/day (prothioconazole-desthio developmental) with 1000 MOE (standard 100-fold for intraspecies and interspecies differences and an additional 10-fold to account for severity of endpoint [malformations at maternally non-toxic doses]).		

Table 2 Toxicology Summary Table—Prothioconazole-desthio

Metabolism—Prothioconazole-desthio
SXX 0665 (prothioconazole-desthio) Rate and extent of absorption and excretion: 90% of administered dose excreted in bile and urine at 48 hours, 5–6% remaining in carcass. Distribution / target organ(s): Autoradiography suggests that desthio and/or its metabolites accumulated in fat more so than plasma, however, the total fraction of administered dose is very small.
Pregnant rat dermal absorption study: 5/dose, pregnant Wistar rats, singly or in multiple doses, 1 or 3 mg/kg orally by gavage, 30 or 100 mg/kg dermally. Dosing was on gestation day 6. Multiple dosing was performed with 9 non-doses and 1 dose at 24-hour intervals. Dermal exposures were for 6 hours followed by 18 hours of non-exposure. Maximum plasma concentrations were similar at 1, 3 and 30 mg/kg (after single or multiple dosing). The maximum plasma concentration differed after single and multiple dermal applications at 100 mg/kg (3× higher after repeat dosing). There was a non-dose-dependent delay in time to achieve maximum concentration when comparing dermal to oral administration. The longest terminal half-life was seen following single dermal application at 100 mg/kg (34.4 hours). The lowest terminal half-life occurred following the 30 mg/kg multiple dermal application (15.6 hours). Repeat doses to the skin were poorly absorbed (approximately 5–10% of dose achieved systemic circulation) which means that a 30 mg/kg dermal dose is roughly equivalent to 1.5 mg/kg orally.

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Acute Studies—Prothioconazole-desthio			
Oral	93.7% a.i. 5 SPF-bred Wistar rats/sex/dose 100, 500 males, 1000 females, 2000, 2500 males, 3150, 4000 mg/kg bw, Cremophor EL 1% vehicle	LD_{50} 2806 mg/kg males 2506 mg/kg females	**100 mg/kg** No mortality ≥ **500 mg/kg** No mortality; piloerection, apathy, staggering gait, laboured breathing, ↑ urine excretion ≥ **1000 mg/kg** No mortality; ↓ motility, spastic gait, laboured urination ≥ **2000 mg/kg** 1 female died, ↓ bw, emaciation, poor reflexes, atony, soft feces, lightly coloured feces, narrowed palpebral fissure, bloody snout, distended patchy lungs with fluid content and dark colour ≥ **2500 mg/kg** 2 males died, pallor, enlarged and discoloured liver, dark spleen, pale kidney and red mucoid contents of stomach and small intestine ≥ **3150 mg/kg** 3 males died (days 9–10), 4 female died (day 9–13), patchy spleen and kidneys, reddened glandular stomach **4000 mg/kg** 10/10 died, salivation, lacrimation, red incrusted eyelids, prostrate, pale liver lobulated with multiple light zone, pale spleen

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Oral	94.7% a.i. 5 SPF-bred NMRI mice/sex/dose 100, 500 males, 1000, 2000, 3150 (10/sex/dose), 4000 (10/sex/dose), 5000 mg/kg bw, Cremophor EL 1% vehicle	LD_{50} 2235 mg/kg males 3459 mg/kg females	**100 mg/kg** No mortality **≥ 500 mg/kg** No mortality; piloerection, apathy, ↓ motility, staggering gait, spasmodic state, laboured breathing, narrowed palpebral fissure **≥ 1000 mg/kg** 1/5 male died; prostration, patchy lungs, stomach/small intestine with red, mucoid contents **≥ 2000 mg/kg** 1/5 males, 1/5 females died, distended abdomen, temporary rolling over, distended lungs **≥ 3150 mg/kg** 9/10 males, 5/10 females died, patchy liver, spleen, and kidneys, bladder engorged with urine **≥ 4000 mg/kg** 3/10 males, 3/10 females died, lacrimation, lobulated, enlarged, and pale liver **5000 mg/kg** 5/5 males, 3/5 females died
Acute Intraperitoneal	94% a.i. 5 SPF-bred Wistar rats/sex (1% v/v Cremophor EL) 10, 100, 355, 400, 450, 500, 800 or 1000 mg/kg bw	Estimated intraperitoneal LD_{50} males 450 and 500 mg/kg, females 632 mg/kg	**100 mg/kg** Signs of apathy, laboured breathing, ↓ motility, staggering gait, atony in males (these signs in females at doses above 100 mg/kg) **> 100 mg/kg** Piloerection, poor or no reflexes, lying on the side, spasmodic state, transient convulsions, stretched legs and lacrimation **≥ 355 mg/kg** Whitish liver surface in males **≥ 500 mg/kg** Pale organs and patchy and/or distended lungs in males **≥ 800 mg/kg** Mucid contents in the small intestine in females
Dermal	93.7% a.i. 5 SPF-bred Wistar rats/sex, 5000 mg/kg, saline vehicle	LD_{50} > 5000 mg/kg	No mortality Slight body-weight loss in females
Inhalation	93.7% a.i. 5 SPF-bred Wistar rats/sex/dose at 0 or 5.077 mg/L	LC_{50} > 5.077 mg/L	No mortality

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Eye Irritation	95.4% a.i. 3 female HC:New Zealand white rabbits, 100 µL, washed at 24 hours	Moderate iritis from 24 to 72 hours MIS 4/110 at 1 hour MAS 1.3/110 at 24, 48 and 72 hours	Eye irritation scores were not zero at 72 hours, so category increased one category to mildly irritating
Skin Irritation	95.4% a.i. 3 female HC:New Zealand white rabbits, 500 mg including moisture, 4 hours	No irritation	Non-irritating
Skin Sensitization (Buehler)	94.7% a.i. 10 male Bor:DHPW guinea pigs (2 × 5 control) 60% patch inductions 60% patch challenge	No responses	Not a sensitizer
Short-Term Toxicity—Prothioconazole-desthio			
5-day inhalation Range finding	10 Wistar rats/sex/dose, 0, 100, 450, 2500 mg/m^3 (analytically 0, 10.7, 53.9, 234.7 mg/m^3) 6 hours/day, 5 days/week 5 rats/sex/dose killed day 7 or after 2-week recovery	Not applicable	**234.7 mg/m^3** Slight ↑ transaminase, ALP and clotting time in males
28-day, inhalation Unacceptable	10 Wistar rats/sex/dose, 0, 11.3, 46.8, 228.4 mg/m^3, 6 hours/day, 5 days/week (approximately 0, 4.1, 16.8, 82.2 mg/kg bw/day)	NOAEL 82.2 mg/kg bw/day LOAEL not determined	No treatment-related effects

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
28-day, dietary	10 Bor:WISW (Spf-Cpb) rats/sex/dose (1% peanut oil) 0, 100, 300, 1000 ppm (0, 11/11, 34/38, 117/121 mg/kg bw/day)	NOAEL 11 mg/kg bw/day in males, not determined in females LOAEL 34 mg/kg bw/day in males 11 mg/kg bw/day in females	≥ **11/11 mg/kg bw/day** ↑ absolute and relative ovary weight Enlarged ovaries with clear watery fluid Fatty infiltration of the liver in males (0, 2, 1, 5) ↑ absolute and relative pituitary weight in females ≥ **34/38 mg/kg bw/day** ↑ P450 in males ↑ liver triglycerides in males ↑ absolute and relative liver weight in males ↑ absolute and relative adrenal weight in females ↑ incidence of dams with > 3 tertiary follicles in ovaries (1/5, 1/5, 2/5, 3/5) ↑ incidence stromal edema of ovaries (2/5, 2/5, 5/5, 4/5) **117/121 mg/kg bw/day** ↓ creatinine ↓ bilirubin in males ↓ blood triglycerides in males ↑ cholesterol in females ↑ *N*-demethyltransferase in females ↓ *O*-demethyltransferase ↑ P450 in females ↓ T4 in males ↑ absolute and relative liver weight in females ↑ absolute and relative kidney weight in females

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
13-week mouse dietary	10 $B6C3F_1$ mice/sex/dose (1% peanut oil) 0, 40, 200, 1000 or 5000 ppm (0/0, 11.5/16.0, 58.9/79.5, 294.0/392.3 or 1454/2073 mg/kg bw/day males/females—with 5000 ppm equivalent calculated by reviewer)	NOAEL < 11.5/16.0 mg/kg bw/day males/females LOAEL 11.5/16.0 mg/kg bw/day males/females	≥ **11.5/16.0 mg/kg bw/day** ↓ bwg (21, 26, 71% in males, 22, 6, 32% in females) ↑ EROD in males ↑ ECOD, ALD (males/females) ↑ hepatocellular hypertrophy in females ≥ **58.9/79.5 mg/kg bw/day** ↑ EROD in females ↑ ALP in males ↑ absolute and relative liver weights in males ↑ single cell necrosis ↑ hepatocellular hypertrophy in males ↑ severity and incidence of hemorrhagic degeneration of the corpora lutea in females (1, 2, 4, 9) **294.0/392.3 mg/kg bw/day** ↑ ASAT, ALT, GLDH and triglyceride ↓ cholesterol ↑ triglyceride ↑ GST in females ↑ absolute and relative liver weights in females ↑ accentuated lobulation in liver in males ↑ periacinar hepatocytic fatty vacuolation in males ↓ erythrocytes, Hb, Hct, leukocytes and PLT counts in males ↑ MCH, MCHC in males ↓ testes weight (absolute ↓ 15%, relative ↓ 8%) **1454/2073 mg/kg bw/day** animals died/killed within one week of treatment ↑ ploidy in livers in males abnormal contents in the cecum, colon, duodenum, jejunum and rectum, ↑ emaciation changed areas of glandular mucosa of the stomach (1 male, 3 females)

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
14-week, dietary	10 Wistar rats/sex/dose (1% peanut oil) 0, 30, 125, 500, 2000 ppm (0, 2.2/3.0, 9.6/12.5, 36.9/50.7, 161.9/210.8 mg/kg bw/day), also 5-week recovery groups 10/sex/dose, 0, 2000 ppm (0, 162.2/219.1 mg/kg bw/day) Terminal body weight and food consumption for control animals: bw = 358 g FC = 22 g/day	NOAEL 2.2/3.0 mg/kg bw/day LOAEL 9.6/12.5 mg/kg bw/day	**≥ 2.2/3.0 mg/kg bw/day** ↓ bilirubin in females week 14 ↓ liver triglyceride in females week 15 **≥ 9.6/12.5 mg/kg bw/day** ↑ P450 in females ↑ incidence and severity of hepatocellular hypertrophy, vacuolation, and midzonal centrilobular fatty change in males ↓ triglyceride in males week 5 **≥ 36.9/50.7 mg/kg bw/day** ↓ bilirubin in males week 14 ↓ triglycerides in males week 14 ↑ absolute and relative liver weight ↑ amino-N-demethylase in females ↑ P-nitroanisole-O-demethylase in females ↑ P450 in males Pale and/or enlarged livers in males ↑ incidence and severity of hepatocellular hypertrophy in females ↓ T4 (24–30% 5 weeks, 47–70% 14 weeks) in males **161.9/210.8 mg/kg bw/day, 14-week sacrifice** ↓ bw, bwg in males Protein and ketones in urine, week 4 in males ↑ ASAT, ALT, ALP in males ↑ ALT in females ↑ cholesterol in females ↑ P-nitroanisole-O-demethylase in males ↓ liver triglyceride in males week 15 Enlarged livers in males/females ↑ absolute and relative ovary weight **162.2/219.1 mg/kg bw/day, recovery** ↑ P-nitroanisole-O-demethylase in males ↓ liver triglyceride in males Hepatocellular hypertrophy in males, severity improved

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
39-day dog, dietary Range-finding (1 female pregnant at study end in 30 mg/kg bw group, small sample size)	2 Beagle dogs/sex/dose (no vehicle) 0, 10, 100/5000 or 1000 ppm (0, 0.3, 3/150 or 30 mg/kg bw/day) *100 ppm increased to 5000 ppm on day 26*	Not applicable	**≥ 0.3 mg/kg bw/day** ↓ absolute and relative uterus/oviduct weights (unknown toxicological significance) Round cell infiltration in adrenal (0, 1, 1, 1) **3/150 mg/kg bw/day** ↓ bw/FC after initiation of 150 mg/kg bw/day (bw lower at end of study than initiation) ↑ EROD in males ↑ urea ↑ megakaryocytes (in 1 female with thymic atrophy) **30 mg/kg bw/day** ↑ hepatocyte optical density ↑ iron pigmentation in spleen **3/150 and 30 mg/kg bw/day** ↑ absolute and relative liver and thyroid weights ↑ cytoplasmic change in liver ↑ ECOD, ALD, EH, UDPGT activation ↑ *N*-demethylase, *O*-demethylase, P450 ↓ cellularity in bone marrow of femur and sternum
90-day dog, dietary Supplemental (liver investigations not GLP, no organ weights for gallbladder, thymus, epididymis, uterus and parathyroid, histology slide exam non-GLP)	4 Beagle dogs/sex/dose (no vehicle) 0, 40, 200 or 1000 ppm (0, 1.58/1.62, 7.81/8.53 or 37.79/42.75 mg/kg bw/day males/females)	NOAEL 1000 ppm (37.79/42.75 mg/kg bw/day males/females) (highest dose tested) LOAEL not determined	N.B. Liver changes considered adaptive and not adverse. **37.79/42.75 mg/kg bw/day** ↑ absolute and relative liver weights in females ↑ *N*-demethylase, *O*-demethylase ↑ P450 in males Cytoplasmic change in liver (3/4 males, 4/4 females)

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
30-week dog, dietary Supplemental (study terminated prior to 52 weeks, no authorized study plan for necropsy, urine investigations, liver investigations and histopathological exam and slides, brains not examined histologically)	4 Beagle dogs/sex/dose (no vehicle) 0, 40, 300 or 2000 ppm (0, 1.35/1.55, 10.1/11.1 and 69.9/77.1 mg/kg bw/day males/females)	NOAEL 2000 ppm (69.9/77.1 mg/kg bw/day males/females) (highest dose tested) LOAEL not determined	N.B. Liver changes considered adaptive and not adverse. **69.9/77.1 mg/kg bw/day** ↑ absolute and relative (to bw and brain weight) liver weights in males ↑ relative liver weight in females ↑ *N*-demethylase, *O*-demethylase, P450 ↑ ALP ↓ T4 (6–69% males, 16–70% females), no relationship to chronology, up and down throughout ↑ relative (to brain weight) heart weight (↑ 36%) in males ↑ mild inflammatory infiltration between the heart muscle and aorta in males (2/4)

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Chronic Toxicity and Oncogenicity—Prothioconazole-desthio			
2-year rat, dietary	50 Bor:WISW (SPF CPB) Wistar rats/sex/dose (10/sex/dose for interim kill at week 52) (1% peanut oil) 0, 20 , 140 or 980 ppm (0, 1.1/1.6, 8.0/11.2 or 57.6/77.4 mg/kg bw/day for males/females)	NOAEL 1.1/1.6 mg/kg bw/day (males/females) LOAEL 8.0/11.2 mg/kg bw/day (males/females)	≥ **8.0/11.21 mg/kg bw/day** ↑ liver discolouration (week 52 in males) ↑ hepatocellular vacuolation (week 52/104 in males, week 104 in females) ↑ centrilobular fatty change (week 52/104 in males) ↑ periportal fatty change (week 52 in females) ↑ single cell fatty change (week 104) ↓ T4 (week 104 in males) ↑ number of corpora lutea in females at week 104 ↑ pituitary cysts in males (3, 2, 9, 11) (week 104) ↑ cortical vacuolation in adrenal gland in males (week 104) **57.6/77.4 mg/kg bw/day** ↓ bw (3–9% females), ↓ bwg (16–40% females) ↑ absolute (week 52/104 in males) and relative (week 52/104) liver weights ↑ incidence of enlarged livers in males ↑ incidence of single cell necrosis (week 52 in males) ↑ cytoplasmic change in liver (week 104 in males, week 52/104 in females) ↑ hepatocellular hypertrophy (week 104) ↓ T3 (week 53/104 in females) ↑ incidence of hypertrophy of follicular epithelium in thyroid (week 52 in females) ↑ colloidal mineralization in thyroid (week 52 in males, week 52/104 in females) ↑ absolute and relative ovary weights (week 104 in females) ↑ ovarian follicular cysts in females week 104 (12, 7, 16, 23) ↑ incidence focal adrenocortical hyperplasia in females week 104 (3, 3, 4, 10) No evidence of carcinogenicity

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
2-year mouse, dietary	50 B6C3F1 mice/sex/dose (10 mice/sex/dose for sacrifice at 12 months) (1% peanut oil) 0, 12.5, 50 or 200 ppm (0, 3.1/5.1, 12.8/20.3 or 51.7/80.0 mg/kg bw/day) (males/females)	NOAEL 12.8/20.3 mg/kg bw/day (males/females) LOAEL 51.7/80.0 mg/kg bw/day (males/females) No evidence of carcinogenicity	N.B. Liver and kidney changes considered treatment-related and adverse at high dose. **≥ 3.1/5.1 mg/kg bw/day** ↑ periacinar fat staining (week 104 in females) ↓ urea levels in blood in males ↓ triglycerides in males **≥ 12.8/20.3, mg/kg bw/day** ↑ periacinar fat staining (week 104 in females, 11, 21, 28, 25; week 52 in males, 1,1, 3, 6) ↑ periacinar hypertrophy with cytoplasmic change in hepatocytes (week 52 in females) (0, 0, 3, 5) **51.7/80.0 mg/kg bw/day** ↓ bw in males ↓ cholesterol in males, triglycerides ↑ glucose (week 53 in males), ↓ glucose (week 105 in females) ↑ fine vesicular vacuolation in hepatocytes (week 52 in males) (1, 1, 3, 6) ↑ periacinar fat staining (week 104 in males) (20, 17, 22, 32) ↑ eosinophilic droplets in the cortical tubules week 104 in females (1, 1, 2, 3) ↑ absolute and relative liver weights ↑ absolute and relative kidney weight in females

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Reproduction and Developmental Toxicity—Prothioconazole-desthio			
Multigeneration reproduction, dietary	30 Sprague-Dawley rats/sex/dose 0, 40, 160, 640 ppm (1% corn oil) Equivalent to P males 2.9, 11.4, 45.6 P females 2.5, 10.1, 40.7 F_1 males 2.5, 9.5, 39.6 F_1 females 2.4, 9.9, 41.7	**Parental** NOAEL 9.5 mg/kg bw/day LOAEL 39.6 mg/kg bw/day **Offspring** NOAEL 9.5 mg/kg bw/day LOAEL 39.6 mg/kg bw/day **Reproductive** NOAEL 9.5 mg/kg bw/day LOAEL 39.6 mg/kg bw/day	**≥ 9.5 mg/kg bw/day** **P adults** ↑ incidence and/or severity of multifocal hepatocellular cytoplasmic vacuolation in males **F_1 adults** ↑ absolute ovary weight ↑ incidence and/or severity of multifocal hepatocellular cytoplasmic vacuolation in males **39.6 mg/kg bw/day** **P adults** One dam from each of control and high doses died due to dystocia, three high dose dams were euthanized for the same Dystocia (1, 0, 0, 4) ↑ relative liver weight in males ↑ incidence and/or severity of multifocal hepatocellular cytoplasmic vacuolation ↑ liver necrosis in females ↓ food consumption during lactation in females **F_1 adults** Three dams died due to dystocia Dystocia (1, 0, 0, 3) ↑ relative liver weight ↑ absolute and relative ovary weight in females ↑ incidence and/or severity of multifocal hepatocellular cytoplasmic vacuolation ↑ liver necrosis in females ↑ mean number of antral follicles in ovaries in females ↓ food consumption during lactation in females **F_1 pups** ↑ incidence cannibalized and/or missing ↓ viability index ↓ bw ↑ incidence enlarged liver, cleft palate, red kidney zones, dilated renal pelvis, dilated ureters, distended bladder **F_2 pups** ↑ incidence cannibalized and/or missing ↑ incidence weak and unthrifty ↓ viability index ↓ bw ↑ incidence dilated renal pelvis

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Developmental toxicity, gavage	25 female Wistar rats/dose 0, 10, 30, 100 mg/kg bw/day, (bidistilled water with 0.5% Cremophor EL) GD 6–15 Additional subgroup of 10/dose were assessed for liver toxicity and sacrificed GD 16	**Maternal** NOAEL 30 mg/kg bw/day LOAEL 100 mg/kg bw/day **Developmental** NOAEL not determined LOAEL 10 mg/kg bw/day Sensitivity of young	**Maternal** **100 mg/kg bw/day** ↓ uncorrected bwg (↓ 11%) ↓ FC ↑ absolute and relative liver weight (subgroup) ↑ severity of inflammatory foci ↑ centrilobular hypertrophy and fatty change (subgroup) **Developmental** ≥ **10 mg/kg bw/day** Supernumerary ribs **100 mg/kg bw/day** ↑ postimplantation loss and resorptions ↓ mean number of live fetuses, slight Incomplete or unossified digits, sternebrae, vertebrae, crania Cleft palate
Developmental toxicity, gavage Supplemental (non-guideline)	30 female Wistar rats/dose (0.5% Cremophor EL in bidistilled water) GD 6–15 0 or 30 mg/kg bw/day Split into 2 groups of 15, half for cesarian section (killed GD 20), half for rearing (sacrificed postpartum days 42–44) 9 dams were added to the treatment group due to 1 death and high pup mortality in the rearing subgroup	Not applicable	**Maternal** **30 mg/kg bw/day** Two cases of engorged placentas ↓ rearing index due to total litter loss of 5 litters within 6 days of birth Increased placental weights agreeing with engorged placentas in cesarian group **Developmental** **Cesarian** **30 mg/kg bw/day** Skeletal dysplasias of the radius and ulna (100% of treated) Humeral dysplasia (5 fetuses in 3 litters) Cleft palate (10 fetuses in 3 litters) Delayed ossification of sternum, ribs, hyoid Supernumerary (14^{th}) ribs (15.3% c, 100% t) Supernumerary (15^{th}) ribs (0 c, 3% treated) Supernumerary (16^{th}) ribs (0 c, 1.5% t) **Rearing** **30 mg/kg bw/day** ↑ emaciated pups ↑ pups with decreased body temperature Supernumerary (14^{th}) ribs (3.7% c, 31.9% t) No 15^{th} or 16^{th} ribs found Not completely reversible

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Developmental toxicity, gavage Supplemental: only 2 dose levels, meant as a range finding—limited observations in dams (only evaluated appearance, behaviour and bwg in dams)	25 female Wistar rats/dose (0.5% aqueous Cremophor EL) 0 or 100 mg/kg bw/day GD 6–15	Not applicable	**Maternal** **100 mg/kg bw/day** ↑ placental weights **Developmental** **100 mg/kg bw/day** ↑ incidence of malformations and variations, dysplasia, cryptorchidism, macroglossia, cleft palate, hydronephrosis, rib abnormalities (eminence), angled mouth and edema. Multiple malformations were noted in a number of fetuses, most commonly consisting of combinations of macroglossia, cleft palate and dysplasia
Developmental toxicity, gavage Supplemental: only 3 dose levels—meant to find NOAEL for rib effects	25 female Wistar rats/dose (0.5% Cremophor EL in bidistilled water) 0, 1 or 3 mg/kg bw/day GD 6–15	**Maternal** NOAEL 30 mg/kg bw/day (from supplemental study) **Developmental** NOAEL 3 mg/kg bw/day LOAEL 10 mg/kg bw/day (from supplemental study)	**Maternal** No treatment-related adverse effects **Developmental** **3 mg/kg bw/day** ↑ incidence of supernumerary ribs compared to concurrent controls (within historical control and control group) (incidental)
Developmental toxicity, dermal	25 female Bor/WISW ([SPF Cpb]) Wistar rats/dose (suspension with 1% aqueous Cremophor EL), 6 hours/day 0, 100, 300 or 1000 mg/kg bw/day GD 6–15	**Maternal** NOAEL 1000 mg/kg bw/day (highest dose tested) LOAEL not determined **Developmental** NOAEL 30 mg/kg bw/day (from supplemental study) LOAEL 100 mg/kg bw/day Sensitivity of young	**Maternal** No treatment-related adverse effects **Developmental** **≥ 100 mg/kg bw/day** ↑ supernumerary 14th rib **≥ 300 mg/kg bw/day** ↑ microphthalmia (0, 0, 2, 2) (compared with concurrent and historical controls) **1000 mg/kg bw/day** Hydrocephaly, hydronephrosis, macroglossia ↑ tubular bone dysplasia ↑ 15th rib (compared to concurrent controls—no historical control data)

Study	Species, Strain and Doses	NOAEL and LOAEL mg/kg bw/day	Target Organ, Significant Effects, Comments
Developmental toxicity, dermal Supplemental: only 3 dose levels—meant to find NOAEL for rib effects	25 female Bor/WISW ([SPF Cpb]) Wistar rats/dose (suspension with 1% aqueous Cremophor EL), 6 hours/day 0, 10 or 30 mg/kg bw/day (0, 5 or 15 mg/mL) GD 6–15	**Maternal** NOAEL 30 mg/kg bw/day (highest dose tested) LOAEL not determined **Developmental** NOAEL 30 mg/kg bw/day (highest dose tested) LOAEL not determined	**Maternal** No treatment-related adverse effects **Developmental** No treatment-related adverse effects
Developmental toxicity, gavage	15 female Himalayan rabbits/dose (0.5% aqueous Cremophor EL) 0, 2, 10, 50 mg/kg bw/day	**Maternal** NOAEL 10 mg/kg bw/day LOAEL 50 mg/kg bw/day **Developmental** NOAEL 2 mg/kg bw/day LOAEL 10 mg/kg bw/day Sensitivity of young Teratogenic at non-maternally toxic doses	**Maternal** ≥ **10 mg/kg bw/day** No treatment-related adverse effects **50 mg/kg bw/day** ↓ bwg ↓ food consumption (↓ 11.4%, not statistically significant) Hepatocyte hypertrophy ↓ gestation rate ↑ resorptions ↓ number of fetuses (resorptions) **Developmental** ≥ **10 mg/kg bw/day** Arthrogryposis (permanently contracted joint) (0, 1, 5 [in 4 litters], 1 [historical 1]) Multiple malformations (0, 0, 2, 0 [historical 1]) **50 mg/kg bw/day** Cleft palate (0, 0, 0, 5) ↑ postimplantation loss

Study	Species and Strain or Cell Type and Concentrations or Doses	Results
Genotoxicity—Prothioconazole-desthio		
Gene mutations in bacteria	Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 150–2400 µg/plate (plate incorporation and pre-incubation); with and without activation	Negative
Gene mutations in mammalian cells in vitro	Chinese hamster lung V79 cells (HGPRT locus) 12.5–250 µg/mL µg/plate -S9 50–500 µg/mL with activation +S9	Negative

Study	Species and Strain or Cell Type and Concentrations or Doses		Results
Unscheduled DNA synthesis in vitro	Primary rat hepatocytes 5–60 µg/mL (18–20 hours)		Negative
Chromosome aberrations in vitro	Chinese hamster lung V79 cells 5, 25, 125 µg/mL ± S9 for 8, 24 and 30-hour harvests		Negative
Micronucleus assay in vivo	Male and female Bor:NMRI(SPF Han) mice 350 mg/kg (single intraperitoneal dose; bone marrow harvested 16, 24 and 48 hours postdosing)		Negative
Special Studies—Prothioconazole-desthio			
Liver foci test with initiation and regeneration, dietary	5 Wistar rats/sex/dose, 0, 980 ppm with an initiator, *N*-nitrosomorpholine (NNM) and a regenerative cellular proliferation inducer, D-galactosamine (DGA) given to some groups (1% peanut oil)	Supplemental, supports lack of liver tumours, but also supports findings in other studies such as vacuolation and enzyme induction in the liver	↑ foci of altered hepatocytes (FAH) at 6 weeks ↓ FAH at 12 weeks Desthio with NNM and DGA ↑ FAH slightly compared to controls Severe cytoplasmic vacuolation at 12 weeks in the zone II hepatocytes in males Isolated cellular destruction and mitosis of parenchymal cells in males

Study	Species and Strain or Cell Type and Concentrations or Doses		Results
Developmental neurotoxicity study, dietary Deficiencies: 1) Brain measurements reported combined left/right 2) Positive control data not provided 3) FOB procedure not well described 4) Data from litters culled PND 4 excluded from PND 0 reporting 5) Nerve pathology and brain morph not assessed in mid and low doses 6) Learning and memory trials not summarized properly 7) Lack of motor activity habituation at PND 60 in females 8) Sacrifice day of dystocia dams unclear 9) Fate and pregnancy status of one female unknown	30 females Wistar Hannover Crl:WI (Glx/BRL/Han) IGS BR rats 0, 40, 160, 500 ppm (0, 3.6, 15.1, 43.3 mg/kg bw/day during gestation and 0, 8.1, 35.7 and 104.6 during lactation) FOB on 30 dams/dose on GDs 13 and 20 FOB on 10 dams/dose on LDs 11 and 21 FOB on 16 pups/sex/dose on PNDs 4, 11, 21, 35, 45 and 60 While not a deficiency, the water maze results were poorly presented and suffered from high variability.	**Maternal** NOAEL 3.6 mg/kg bw/day LOAEL 15.1 mg/kg bw/day **Developmental** NOAEL 3.6 mg/kg bw/day LOAEL 15.1 mg/kg bw/day **Neurotoxicity** NOAEL not determined LOAEL not determined—critical parameters not measured	**Maternal** **≥ 15.1 mg/kg bw/day** ↑ stillborn pups (0, 0, 3, 3) **43.3 mg/kg bw/day** 3 dams sacrificed due to dystocia ↑ gestation time ↓ mean pups per litter (slight) **Developmental** **≥ 15.1 mg/kg bw/day** ↑ stillborn pups (0, 0, 3, 3) Progressive malocclusion and deviated snout (0, 0, 3, 11) **43.3 mg/kg bw/day** ↓ mean pups per litter (slight) ↑ total motor activity at PND 13 ↑ auditory startle at PND 22 in males ↑ lesions of the peripheral nerves (mid and low doses not evaluated) ↑ corpus callosum in females (19–25%) (mid and low doses not evaluated)
Compound-Induced Mortality Acute mortality at doses ≥ 2000 mg/kg in rats and 1000 mg/kg in mice. Deaths due to dystocia in the rat two-generation reproduction study at 39.6 mg/kg bw/day. Potential slight increase in stillborn pups at 15.1 mg/kg bw/day in the rat developmental neurotoxicity study.			

Appendix II Residues

Table 1 Integrated Food Residue Chemistry Summary

Directions for Use of Prothioconazole						
Trade Name	Application Timing, Type and Equipment	Application Rate [g a.i./ha]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate [g a.i./ha]	PHI (days)	Use Directions and Limitations
Barley						
Proline® 480 SC Foliar Fungicide	Postemergence Broadcast foliar Ground	150–200	1	200	30	*Fusarium head blight:* For barley, apply when 70–100% heads on the main stem are fully emerged to 3 days after full head emergence. Apply at the highest rate where disease pressure is expected to be high. Apply a non-ionic surfactant.
Proline® 480 SC Foliar Fungicide	Postemergence Broadcast foliar Ground	150	1	150	30	*Leaf and stem diseases:* Apply when earliest disease symptoms appear on leaves or stems.
Maximum of two applications of Proline® 480 SC Foliar Fungicide per year.						
Wheat						
Proline® 480 SC Foliar Fungicide	Postemergence Broadcast foliar Ground	150– 200	1	200	30	*Fusarium head blight:* For wheat, apply when 75% of wheat heads on main stem are fully emerged, to when 50% of heads on main stem are in flower. Apply at the highest rate where disease pressure is expected to be high. Apply a non-ionic surfactant.
Proline® 480 SC Foliar Fungicide	Postemergence Broadcast foliar Ground	150–200	1	200	30	*Septoria glume blotch:* Apply when earliest disease symptoms appear on leaves or stems.
Proline® 480 SC Foliar Fungicide	Postemergence Broadcast foliar Ground	150	1	150	30	*Septoria leaf blotch, tan spot and leaf rust:* Apply when earliest disease symptoms appear on leaves or stems.
Maximum of two applications of Proline® 480 SC Foliar Fungicide per year. One application to control Septoria leaf blotch, tan spot and leaf rust; another application to control fusarium head blight and Septoria glume blotch.						

Directions for Use of Prothioconazole						
Trade Name	Application Timing, Type and Equipment	Application Rate [g a.i./ha]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate [g a.i./ha]	PHI (days)	Use Directions and Limitations
Canola, Rapeseed (*Brassica napus* and *Brassica rapa*), Oriental mustard (*Brassica juncea*)						
Proline® 480 SC Foliar Fungicide	Postemergence Broadcast foliar Ground or aerial	150–175	1	175	36	Apply during the 20% to 40% bloom stage at 150 g a.i./ha rate. Use 175 g a.i./ha rate if field has history of disease or dense crop stands. Use of a spray surfactant (at the lowest rate) is recommended.
Chickpeas and Lentils						
Proline® 480 SC Foliar Fungicide	Postemergence Broadcast foliar Ground	Chickpeas 150–200 Lentils 150–200	Chickpeas 3 Lentils 2	Chickpeas 600 Lentils 400	7	Apply at the first sign of disease. A 10- to 14-day retreatment interval is proposed. Use of a spray surfactant (at the lowest rate) is recommended.

METHODS FOR RESIDUE ANALYSIS

An LC-MS/MS method was developed and proposed for data gathering and enforcement purposes. In plant matrices, an oxidative extraction procedure converts prothioconazole residues to a mixture of prothioconazole-desthio and prothioconazole sulfonic acid. The results are reported as prothioconazole equivalents. In animal matrices, extracts are acid hydrolyzed and residues are reported as prothioconazole equivalents (prothioconazole, prothioconazole-desthio, prothioconazole-4-hydroxy). The method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method LOQ. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. Adequate extraction efficiencies were demonstrated using radio wheat forage, sugarbeet tops, goat milk, goat liver, goat muscle and goat fat analyzed with the enforcement method. Based on the results of testing, the multiresidue methods are not appropriate for determining prothioconazole residue definition, or for determining residues of triazole, triazolylalanine or triazolylacetic acid.

Matrix	Method ID	Analyte	Method Type	LOQ (ppm)
Plant	RPA JA/03/01	Prothioconazole, prothioconazole sulfonic acid and prothioconazole-desthio	LC-MS/MS[1]	0.02 ppm for canola seed, peanut nutmeat and wheat grain; 0.05 ppm for dried peas, wheat forage, wheat hay and wheat straw.
Plant (triazole)	No method ID. Bayer report No. G200598	1*H*-1,2,4-triazole, triazolylalanine and triazolylacetic acid	LC-MS/MS[1]	0.01–0.05 ppm for 1*H*-1,2,4-triazole; 0.01–1.5 ppm for triazolylalanine and triazolylacetic acid
Animal	No method ID. Bayer report No. 200537	Prothioconazole, prothioconazole-desthio, prothioconazole-4-hydroxy and conjugates that may be converted to these compounds by acid hydrolysis	LC-MS/MS[2]	0.005 ppm for each analyte in milk; 0.010 ppm for each analyte in skim milk, cream, muscle, liver and kidney; and 0.050 ppm for each analyte in fat

[1] The ion transitions monitored are prothioconazole sulfonic acid: 390.45-354.45; prothioconazole-desthio: 312.35-125.52.
[2] The ion transitions monitored are prothioconazole: 342-100; prothioconazole-desthio: 312-70; prothioconazole-4-hydroxy: 358-100.

NATURE OF THE RESIDUE IN PLANTS—Wheat Foliar		
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	[Triazole-3,5-^{14}C]-Prothioconazole
Test site	Plants were grown in 1 m^2 planting containers at outdoor test plots.	Plants were grown outdoors in a 2.02 m^2 metal stock tub; the tub was moved into a greenhouse one day prior to application of test substance and was moved outdoors one day after application.
Treatment	The radio test substance was formulated as an EC with formulation blank, then diluted with water and applied using a computer-controlled track sprayer.	The radio test substance was combined with non-radiolabelled prothioconazole, evaporated under a stream of nitrogen, and formulated as a suspension concentrate with formulation blank. The formulated test substance was diluted with water and added to a spray bottle containing additional formulation blank prior to application.
Rate	Two applications at 216 g a.i./ha and 199 g a.i./ha for a total application rate of 415 g a.i./ha.	Two applications at 178 g a.i./ha and 292 g a.i./ha for a total application rate of 470 g a.i./ha.
PHI	Forage: 6 Hay: 26 Grain and straw: 48	Forage: 6 Hay: 29 Grain and straw: 64
Synopsis	The majority of the radioactivity was found in straw (26.74 ppm), forage (10.45 ppm), hay (8.90 ppm), with only 0.08 ppm in grain. Total extractable residues ranged from 83.1 to 98.0% in all wheat matrices. Non-extractable residues were < 4% of the TRRs (0.83 ppm) in forage, hay and straw, and 17% (0.013 ppm) in grain.	The distribution of radioactive residues was highest in hay (11.175 ppm), followed by forage and straw (each at 7.9 ppm). Wheat grain had 4.973 ppm. Total extractable residues were 94.5 to 99.9% with less than 5.5% remaining as non-extractable in all wheat matrices.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	
Forage	Prothioconazole-desthio	Prothioconazole, prothioconazole-α-OH-desthio, prothioconazole-disulfide, prothioconazole-3-OH-desthio prothioconazole-4-OH-desthio, prothioconazole-6-OH-desthio, prothioconazole-triazolinone, prothioconazole sulfonic acid, sum of glucosides of the OH-desthio isomers
Hay	Prothioconazole-desthio	Prothioconazole, prothioconazole-disulfide, prothioconazole-desthio-glucoside, prothioconazole-α-OH-desthio, prothioconazole-3-OH-desthio prothioconazole-4-OH-desthio, prothioconazole-6-OH-desthio, prothioconazole-triazolinone, prothioconazole sulfonic acid, sum of glucosides of the OH-desthio isomers, prothioconazole-α-acetoxy-desthio, benzylpropyldiol glucoside
Straw	Prothioconazole-desthio	Prothioconazole, prothioconazole-disulfide, prothioconazole-desthio-glucoside, prothioconazole-α-OH-desthio, prothioconazole-3-OH-desthio prothioconazole-4-OH-desthio, prothioconazole-6-OH-desthio, prothioconazole-triazolinone, prothioconazole sulfonic acid, sum of glucosides of the OH--desthio isomers, prothioconazole-α-acetoxy-desthio/benzylpropyldiol, benzylpropyldiol glucoside
Grain	Prothioconazole-desthio	Prothioconazole, prothioconazole-α-OH-desthio, prothioconazole-3-OH-desthio/prothioconazole-4-OH-desthio/prothioconazole-6-OH-desthio, prothioconazole-triazolinone, sum of glucosides of the OH-desthio isomers, prothioconazole-disulfide, prothioconazole-α-acetoxy-desthio, benzylpropyldiol glucoside
Radiolabel Position	[Triazole-3,5-^{14}C]-Prothioconazole	
Forage	Prothioconazole-desthio, triazolylalanine	Prothioconazole, prothioconazole-triazolinone, prothioconazole-α-acetoxy-desthio, prothioconazole-OH-desthio, prothioconazole-α-OH-desthio, isomers of prothioconazole-desthiophenyl-cysteine, glucosides and malonyl glucosides of prothioconazole-OH-desthio, prothioconazole-hydroxy-sulfonic acid-glucosides, and prothioconazole-dihydroxydesthiomalonyl-glucoside, prothioconazole-triazolyl-ethanol and its glucoside, triazolylhydroxypropionic acid, triazolylacetic acid

Hay	Prothioconazole-desthio, triazolylalanine	Prothioconazole, prothioconazole-triazolinone, prothioconazole-α-acetoxy-desthio, prothioconazole-OH-desthio, prothioconazole-α-OH-desthio, glucosides and malonyl glucosides of prothioconazole-OH-desthio, glucosides and malonyl glucosides of prothioconazole-OH-desthio, triazolylhydroxypropionic acid, triazolylacetic acid
Straw	None	Prothioconazole, prothioconazole-desthio, prothioconazole-triazolinone, prothioconazole-α-acetoxy-desthio, prothioconazole-OH-desthio, prothioconazole-α-OH-desthio, glucosides and malonyl glucosides of prothioconazole-OH-desthio, prothioconazole-hydroxy-sulfonic acid-glucosides, prothioconazole-trizolyl-ethanol and its glucoside, triazolylhydroxypropionic acid, triazolylacetic acid, triazolylalanine
Grain	Triazolylalanine, triazolylacetic acid	Triazolylhydroxypropionic acid

NATURE OF THE RESIDUE IN PLANTS—Wheat as Seed Treatment	
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole
Test site	In a climate-controlled chamber in the greenhouse
Treatment	The radio test substance was dissolved in acetonitrile and combined with seed in a beaker. The beaker was gently shaken until the acetonitrile dissolved. The seeds were planted on the day of treatment.
Rate	Low rate: 7.3 µg/seed, equivalent to 18.4 g a.i./100 kg seed High rate: 37 µg/seed, equivalent to 93 g a.i./100 kg seed
PHI	57 days (forage), 110 days (hay) and 153 days (straw and grain) after seed treatment/planting

For the low-rate treatment, TRRs were 0.02 ppm in forage and hay, 0.03 in straw and 0.008 ppm in grain. For the high-rate treatment, TRRs were 0.07 ppm (forage), 0.09 ppm (hay), 0.28 ppm (straw) and 0.012 ppm (grain). Total extractable residues were 75.1 to 92.2% in wheat matrices of the high-rate treatment. Unextractable residues represented 7.7 to 25.7% of the TRRs (< 0.02 ppm).

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	
Forage	Prothioconazole-desthio, prothioconazole-3/4-OH-desthio	Prothioconazole, prothioconazole sulfonic acid, prothioconazole-triazolinone, prothioconazole-6-OH-desthio, prothioconazole-α-OH-desthio, disulfide of prothioconazole
Hay	None	Prothioconazole, prothioconazole-desthio, prothioconazole sulfonic acid, prothioconazole-6-OH-desthio, prothioconazole-3/4-OH-desthio, prothioconazole-α-OH-desthio, disulfide of prothioconazole, prothioconazole-α-acetoxy-desthio, benzylpropyldiol glucoside

Straw	Prothioconazole-hydroxy-desthio glucosides	Prothioconazole, prothioconazole-desthio, prothioconazole sulfonic acid, prothioconazole-6-OH-desthio, prothioconazole-3/4-OH-desthio, prothioconazole-α-OH-desthio, prothioconazole-α-acetoxy-desthio, benzylpropyldiol glucoside
NATURE OF THE RESIDUE IN PLANTS—Sugar Beet		
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	[Triazole-3,5-^{14}C]-Prothioconazole
Test site	Plants were started in the greenhouse, then moved outdoors when seedlings were 5.08 cm tall.	Plants were started in the greenhouse, then moved outdoors when seedlings were 5.08 cm tall.
Treatment	The formulated test substance was diluted with water and added to a spray bottle for application.	
Rate	Four applications at 255, 302, 282 and 313 g a.i./ha/application for a total application rate 1152 g a.i./ha.	Four applications at 260, 291, 285 and 321 g a.i./ha/application for a total application rate of 1157 g a.i./ha.
Application timing	Applications were made 100, 114, 128 and 142 days after planting at 14-day retreatment intervals.	
PHI	7 days	
Synopsis	The majority of the TRRs were in the sugar beet tops (4.3 ppm), with only 0.119 ppm in the root. Total extractable residues were 94 to 98%, with less than 6% remaining as unextractable residues.	The majority of the TRRs were in sugar beet tops (5.2 ppm), with only 0.130 ppm in the root. Total extractable residues were 91.7 to 98.4%, with less than 8.4% remaining as unextractable residues.
Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	
Sugar beet tops	Prothioconazole-desthio	Prothioconazole, triazolylalanine, triazolylhydroxy-propionic acid, triazolyl-sulfonic acid-ethanol glucoside and triazolyl-ethanol-glucoside, prothioconazole-desthio-hydroxy-dieneyl-cysteine isomer, triazolyl-ethanol, prothioconazole-hydroxy-sulfonic acid-glucoside isomer, prothioconazole-hydroxy-sulfonic acid-glucoside isomer, prothioconazole-hydroxy-desthio-glucoside isomer, prothioconazole-hydroxy-desthio, prothioconazole-sulfonic acid, prothioconazole-triazolinone
Sugar beet roots	Prothioconazole-desthio, triazolylalanine	Prothioconazole-desthio-hydroxy-dieneyl-cysteine isomer, prothioconazole-triazolinone

Radiolabel Position	[Triazole-3,5-^{14}C]-Prothioconazole	
Sugar beet tops	Prothioconazole-desthio	Prothioconazole-desthio-hydroxy-dieneyl-cysteine isomer, prothioconazole-desthio-hydroxyl-dieneyl-cysteine isomer, prothioconazole-hydroxy-di-sulfonic acid-glucoside, prothioconazole-hydroxy-sulfonic acid-glucoside isomer, prothioconazole-hydroxy-desthio-glucoside isomer, prothioconazole-hydroxy-sulfonic acid-glucoside isomer, prothioconazole-α-hydroxy-desthio, prothioconazole-triazolinone, prothioconazole
Sugar beet roots	Prothioconazole-desthio	Prothioconazole-triazolinone
NATURE OF THE RESIDUE IN PLANTS—Peanut		
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	[Triazole-3.5-^{14}C]-Prothioconazole
Test site	A climate-controlled chamber in a greenhouse.	A climate-controlled chamber in a greenhouse.
Treatment	Applied using a computer-controlled track sprayer.	Applied using a computer-controlled track sprayer.
Rate	Three applications at 297 g a.i./ha; 299 g a.i./ha; 297.3 g a.i./ha for a total application rate of 895 g a.i./ha.	Three applications at approximately 299 g a.i./ha for a total application rate of 897 g a.i./ha.
Timing of applications	Applications were made at 94, 114 and 136 days after planting at BBCH 66, 71 and 75; 20- to 22-day retreatment intervals.	Applications were made at 93, 113 and 134 days after planting at BBCH 66, 71 and 75; 20- to 21-day retreatment intervals.
PHI	21 days	14 days
Synopsis	The majority of the TRRs was in peanut hay (107.51 ppm), with only 0.3 ppm distributed in the nutmeat. Total extractable residues were 93.8% of the TRRs in peanut hay. In nutmeat using hexane reflux, 91.8% of the TRRs was extractable. Extraction of nutmeat by MSPD/microwave resulted in 87.3% of the TRRs as total extractables.	The majority of the TRRs was in peanut hay (47.38 ppm), with 1.4 ppm distributed in the nutmeat. Total extractable residues were 94.6 to 98%, with less than 5.4% remaining as unextractable residues.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Triazole-3,5-^{14}C]-Prothioconazole	
Peanut hay	Prothioconazole-desthio	Prothioconazole, prothioconazole-3-OH-desthio, prothioconazole-4-OH-desthio, prothioconazole-triazolinone, prothioconazole-sulfonic acid, prothioconazole-dimer (disulfide), prothioconazole-desthio-phenyl-cysteine, isomers of prothioconazole-dihydroxydiene and dihydroxyolefin sulfonic acid, glucosides of prothioconazole-OH-desthio isomers, malonyl-glucosides of prothioconazole-OH-desthio isomers, prothioconazole-desthio-dihydroxyolefin-glucosides, prothioconazole-trizolyl-ethanol-glucoside, prothioconazole-trizolyl-ethanol, triazolylalanine, triazolylhydroxypropionic acid, triazolylacetic acid, prothioconazole-3-OH-desthio glucoside, prothioconazole-4-OH-desthio glucoside, prothioconazole-desthio-dihydroxydiene glucoside
Peanut nutmeat	Triazolylalanine, triazolylhydroxypropionic acid	Prothioconazole-desthio, fatty acids, triazolylacetic acid
Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	
Peanut hay	Prothioconazole-desthio, isomers of prothioconazole-hydroxy-desthio-glucosides	Prothioconazole, prothioconazole-3-OH-desthio, prothioconazole-4-OH-desthio, prothioconazole-3/4-OH-desthio*, prothioconazole-triazolinone, prothioconazole-sulfonic acid, disulfide of prothioconazole, isomers of prothioconazole-desthio-hydroxy-dienyl-cysteine, Sum of isomers of prothioconazole-dihydroxy-diene sulfonic acid and prothioconazole-dihydroxy-olefin sulfonic acid, glucosides of prothioconazole-OH-desthio
Peanut nutmeat	Sum of fatty acids, isomers of Prothioconazole-hydroxy-desthio-glucosides	Prothioconazole-sulfonic acid, glucosides of prothioconazole-OH-desthio, isomers of prothioconazole-desthio-hydroxy-dienyl-cysteine
* No discrimination between isomers possible.		
CONFINED ROTATIONAL CROP STUDY—SWISS CHARD, TURNIP, WHEAT		
Radiolabel Position	[Phenyl-UL-^{14}C]-Prothioconazole	[Triazole-3,5-^{14}C]-Prothioconazole
Application method	The test substance was dissolved in acetonitrile and mixed with non prothioconazole, then sprayed onto bare soil.	The test substance was mixed with non prothioconazole, JAU6476 480 SC formulation blank, acetonitrile and water. The test material was then sprayed onto bare soil.
Application rate	578 g a.i./ha	1: 204 g a.i./ha 2: 217 g a.i./ha 3: 201 g a.i./ha 4: 193 g a.i./ha Total: 815 g a.i./ha

Number of applications	1	4
Timing of applications	28, 146 and 269 days prior to planting of rotational crops.	Applications were made 14 days apart, with the last application made 30, 125 and 366 days prior to planting of rotational crops.
PHI (days)	Not applicable	Not applicable
The overall distribution of the total radioactive residues was evaluated in rotational Swiss chard, turnip and wheat commodities. For the phenyl-label study, TRRs were highest in wheat straw and hay at all plantback intervals. For the triazole-label study, TRRs were highest in wheat grain, hay and straw. For the phenyl-label study, total extractables residues were 61 to 87% of the TRRs for Swiss chard, turnip tops and roots. Remaining unextractable residues were 13 to 39% of the TRRs (< 0.009 ppm). In wheat straw, extractable residues were 93.9 to 99% of the TRRs. In wheat hay and forage, extractable residues were 72 to 94% of the TRRs, with unextractable residues accounting for 5.7 to 28.1% of the TRRs (< 0.029 ppm). Only 26.6% of the TRRs were extractable in wheat grain, with 72.7% remaining as unextractable residues (< 0.005 ppm). For the triazole-label study, total extractable residues, in all commodities for all plantback intervals, were 92 to 102%.		
Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	
Swiss chard [28, 146 PBI] [28 PBI] [146 PBI]	Prothioconazole-desthio Glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1) Glucoside of prothioconazole-hydroxy-desthio (isomer 3)	Prothioconazole, prothioconazole-desthio, glucoside of prothioconazole-benzylpropyldiol, prothioconazole sulfonic acid, prothioconazole-triazolinone, prothioconazole-4-hydroxy-desthio, prothioconazole-3-hydroxy-desthio, prothioconazole-α-hydroxy-desthio, prothioconazole-α-acetoxy-desthio, prothioconazole-disulfide, glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1), glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 3)
Turnip top [28, 269 PBI] [28, 146, 269 PBI] [28 PBI]	Prothioconazole-desthio Glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2) Glucoside of prothioconazole-hydroxy-desthio (isomer 3)	Prothioconazole, prothioconazole-desthio, glucoside of prothioconazole-benzylpropyldiol, prothioconazole sulfonic acid, prothioconazole-triazolinone, prothioconazole-4-hydroxy-desthio, prothioconazole-6-hydroxy-desthio, prothioconazole-3-hydroxy-desthio, prothioconazole-α-hydroxy-desthio, prothioconazole-disulfide, prothioconazole-benzylpropyldiol, glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1), glucoside of prothioconazole-hydroxy-desthio (isomer 1), glucoside of prothioconazole-hydroxy-desthio (isomer 3)

Turnip root [28 PBI] [28, 146, 269 PBI]	Prothioconazole-3-hydroxy-desthio, Prothioconazole-4-hydroxy-desthio, Glucoside of prothioconazole-desthio-hydroxy-olefin (isomer 1), glucoside of prothioconazole-desthio-hydroxy-olefin (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 3) Prothioconazole-desthio	Prothioconazole, glucoside of prothioconazole-benzylpropyldiol, prothioconazole-triazolinone, prothioconazole-4-hydroxy-desthio, prothioconazole-6-hydroxy-desthio, prothioconazole-3-hydroxy-desthio, prothioconazole-α-hydroxy-desthio, prothioconazole-disulfide, prothioconazole-benzylpropyldiol, glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1), glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 1), glucoside of prothioconazole-hydroxy-desthio (isomer 3)
Wheat forage [28 PBI] [146, 269 PBI]	Prothioconazole-desthio Glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1), glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2)	Prothioconazole-desthio, glucoside of prothioconazole-benzylpropyldiol, prothioconazole sulfonic acid, prothioconazole-triazolinone, prothioconazole-4-hydroxy-desthio, prothioconazole-6-hydroxy-desthio, prothioconazole-3-hydroxy-desthio, prothioconazole-α-hydroxy-desthio, prothioconazole-α-acetoxy-desthio, prothioconazole-disulfide, glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1), glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 3)
Wheat hay [28, 146 PBI] [28 PBI] [146, 269 PBI] [28, 146, 269 PBI]	Prothioconazole-desthio Prothioconazole sulfonic acid Glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1) Glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2)	Prothioconazole-desthio, prothioconazole sulfonic acid, prothioconazole-triazolinone, prothioconazole-4-hydroxy-desthio, prothioconazole-3-hydroxy-desthio, prothioconazole-α-hydroxy-desthio, prothioconazole-α-acetoxy-desthio, prothioconazole-disulfide, glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1), glucoside of prothioconazole-hydroxy-desthio (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 3)
Wheat straw [269 PBI] [146 PBI]	Prothioconazole sulfonic acid, glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2) Glucoside of prothioconazole-hydroxy-desthio (isomer 2)	Prothioconazole, prothioconazole-desthio, glucoside of prothioconazole-benzylpropyldiol, prothioconazole sulfonic acid, prothioconazole-triazolinone, prothioconazole-6-hydroxy-desthio, prothioconazole-4-hydroxy-desthio, prothioconazole-3-hydroxy-desthio, prothioconazole-α-hydroxy-desthio, prothioconazole-benzylpropyldiol, prothioconazole-α-acetoxy-desthio, prothioconazole-disulfide, glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 1), glucoside of prothioconazole-desthio-dihydroxy-olefin (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 1), glucoside of prothioconazole-hydroxy-desthio (isomer 2), glucoside of prothioconazole-hydroxy-desthio (isomer 3)

Wheat grain [28 PBI]	—	Prothioconazole-desthio, prothioconazole-3-hydroxy-desthio, prothioconazole-4-hydroxy-desthio, prothioconazole-α-hydroxy-desthio
Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Triazole-3,5-^{14}C]-Prothioconazole	
Swiss chard [125 PBI] [30, 125, 366 PBI]	Triazolyacetic acid Triazolylalanine, THPA	Triazolyl-ethanol, prothioconazole-desthio, triazolyacetic acid
Turnip top [30, 125, 366 PBI]	Triazolylalanine	THPA, triazolylacetic acid, triazolyl-ethanol-glucoside, triazolyl-ethanol, prothioconazole-α-hydroxy-desthio, prothioconazole-desthio
Turnip root [30, 125, 366 PBI]	Triazolylalanine	THPA, triazolylacetic acid, triazolyl-ethanol-glucoside, triazolyl-ethanol, prothioconazole-α-hydroxy-desthio, prothioconazole-desthio
Wheat hay [30, 125, 366 PBI]	Triazolylalanine THPA, triazolyacetic acid	Triazolyl-ethanol-glucoside, triazolyl-ethanol, prothioconazole-α-hydroxy-desthio, prothioconazole-desthio
Wheat forage [30, 125, 366 PBI]	Triazolylalanine, THPA	Triazolylacetic acid, triazolyl-ethanol-glucoside, triazolyl-ethanol, prothioconazole-α-hydroxy-desthio, prothioconazole-desthio, triazolylacetic acid/THPA,
Wheat straw [30, 125, 366 PBI]	Triazolylalanine THPA, triazolyacetic acid	Triazolylacetic acid/THPA, triazolyl-ethanol-glucoside, triazolyl-ethanol, prothioconazole-α-hydroxy-desthio, prothioconazole-desthio
Wheat grain [30, 125, 366 PBI]	Triazolylalanine, triazolyacetic acid	THPA

NATURE OF THE RESIDUE IN LAYING HEN

Species	Dose Level		Length of Dosing	Sacrifice
Hen	9.7 mg/kg bw (phenyl)	10.4 mg/kg bw (triazole)	3 consecutive days	5 hours

In the [phenyl-UL-^{14}C]-prothioconazole treated hens, the recovered radioactivity accounted for 79.28% of the administered dose. Approximately 78.42% of the administered dose was eliminated in the excreta. A total of 0.011% of the administered dose was recovered in eggs, while 0.85% was estimated to have been present in the tissues and organs. A significant portion of the administered dose was absorbed from the intestinal tract prior to excretion, as indicated by the high residue concentrations in the kidney and liver. The recovered radioactivity accounted for 66.37% of the administered dose. A large fraction of the administered dose in the [triazole-UL-^{14}C]-prothioconazole-treated hens was eliminated in the excreta (65.61%). A total of 0.014% of the radioactivity was recovered in eggs while 0.75% was present in the tissues and organs.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	
Liver	Prothioconazole-*O*- or -*S*-glucuronide/prothioconazole-3-hydroxy-desthio; prothioconazole	Prothioconazole-desthio-3,4-dihydroxy-dienyl-glucuronide; sulfate conjugate of prothioconazole-hydroxy-desthio; sulfate conjugates of prothioconazole-hydroxy-desthio, prothioconazole-dihydroxy-desthio and prothioconazole-hydroxy-methoxy-desthio; prothioconazole-dihydroxy-diene; prothioconazole-hydroxy-glucuronides; prothioconazole-4-hydroxy-desthio; prothioconazole-*N*-glucuronide; prothioconazole-4-hydroxy; prothioconazole-desthio; prothioconazole-*S*-methyl
Fat	Prothioconazole-*S*-methyl; prothioconazole-desthio; prothioconazole	Prothioconazole-*O*- or -*S*-glucuronide
Muscle	Prothioconazole-*O*- or -*S*-glucuronide; prothioconazole	Prothioconazole-desthio-3,4-dihydroxy-dienyl-glucuronide*; sulfate conjugates of prothioconazole-hydroxy-desthio, prothioconazole-dihydroxy-desthio and prothioconazole-hydroxy-methoxy-desthio; prothioconazole-dihydroxy-diene; prothioconazole-*N*-glucuronide; prothioconazole-4-hydroxy; prothioconazole-desthio; prothioconazole-*S*-methyl
Egg	Prothioconazole-*O*- or -*S*-glucuronide; rothioconazole-desthio	Prothioconazole-4-hydroxy-desthio; Prothioconazole; Prothioconazole-*S*-methyl
Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Triazole-3,5-^{14}C]-Prothioconazole	
Liver	Prothioconazole-*S*-glucuronide/prothioconazole-3-hydroxy-desthio; sulfate conjugates of prothioconazole-hydroxy-desthio, prothioconazole-dihydroxy-desthio and prothioconazole-hydroxy-methoxy-desthio; prothioconazole	1*H*-1,2,4-triazole; thiocyanate; prothioconazole-triazolyl-ethanol; sulfate conjugate of prothioconazole-hydroxy-desthio; prothioconazole-4-hydroxy-desthio; prothioconazole-*N*-glucuronide; prothioconazole-4-hydroxy; prothioconazole-desthio; prothioconazole-*S*-methyl
Fat	Prothioconazole-desthio; prothioconazole; prothioconazole-*S*-methyl	Sulfate conjugates of prothioconazole-hydroxy-desthio, prothioconazole-dihydroxy-desthio and prothioconazole-hydroxy-methoxy-desthio; prothioconazole-*S*-glucuronide; prothioconazole-triazolyl-ethanol; 1*H*-1,2,4-triazole/thiocyanate
Muscle	1*H*-1,2,4-triazole; prothioconazole-triazolyl-ethanol	thiocyanate; Prothioconazole-*S*-glucuronide; Prothioconazole-desthio; Prothioconazole; Prothioconazole-*S*-methyl

Egg	1*H*-1,2,4-triazole; prothioconazole-triazolyl-ethanol; prothioconazole-*S*-glucuronide/prothioconazole-4-hydroxy-desthio/prothioconazole-3-hydroxy-desthio	Thiocyanate; prothioconazole-desthio; prothioconazole; prothioconazole-*S*-methyl

NATURE OF THE RESIDUE IN RUMINANT				
Species	Dose Level		Length of Dosing	Sacrifice
Goat	246 ppm (phenyl)	195 ppm (triazole)	3 consecutive days	5 hours

The recovered radioactivity accounted for 67.57% of the administered dose. A total of 0.02% of the radioactivity was recovered in milk (0.020–0.071 ppm), while 0.96% was present in the tissues and organs (6.092 ppm in liver, 6.762 ppm in kidney, 0.084–0.106 ppm in muscle and 0.149–0.172 ppm in fat). Approximately 66% of the total administered dose was excreted in urine and feces. The remaining administered dose was assumed to be absorbed from the intestinal tract prior to excretion. The recovered radioactivity accounted for 59.52% of the administered dose. A total of 0.03% of the radioactivity was recovered in milk (0.080–0.249 ppm), while 0.74% was present in the tissues and organs (6.248 ppm in liver, 4.507 ppm in kidney, 0.115–0.142 ppm in muscle and 0.109–0.213 ppm in fat). Approximately 58% of the total administered dose was excreted in urine and feces. The remaining administered dose was assumed to be absorbed from the intestinal tract prior to excretion.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Phenyl-^{14}C]-Prothioconazole	
Milk	Prothioconazole-*O*- or -*S*-glucuronide/prothioconazole-3-hydroxy-desthio	Prothioconazole-*N*-glucuronide, prothioconazole-4-hydroxy, prothioconazole-desthio, prothioconazole, prothioconazole-desthio-dihydroxy-diene, prothioconazole-4-hydroxy-desthio-glucuronide/ prothioconazole-dihydroxy-desthio-glucuronide/prothioconazole-hydroxymethoxy-desthio-glucuronide, prothioconazole-dihydroxy-diene, prothioconazole-desthio-glucuronide
Liver	Prothioconazole-*O*- or -*S*-glucuronide/prothioconazole-3-hydroxy-desthio, prothioconazole-4-hydroxy, prothioconazole	Prothioconazole-hydroxy-glucuronide, prothioconazole-4-hydroxy-desthio, prothioconazole-*N*-glucuronide, prothioconazole-desthio, prothioconazole-desthio-3,4-dihydroxy-dienyl-glucuronide, prothioconazole-desthio-dihydroxy-diene, prothioconazole-4-hydroxy-glucuronide
Kidney	Prothioconazole-*O*- or -*S*-glucuronide/prothioconazole-3-hydroxy-desthio, prothioconazole	Prothioconazole-4-hydroxy, prothioconazole-*N*-glucuronide, prothioconazole-desthio, prothioconazole-hydroxy-glucuronide, prothioconazole-4-hydroxy-glucuronide
Muscle	Prothioconazole-*O*- or -*S*-glucuronide/prothioconazole-3-hydroxy-desthio, prothioconazole	Prothioconazole-hydroxy-glucuronide, Prothioconazole-4-hydroxy, prothioconazole-*N*-glucuronide, prothioconazole-desthio, prothioconazole-4-hydroxy-glucuronide
Fat	Prothioconazole-*O*- or -*S*-glucuronide/prothioconazole-3-hydroxy-desthio, prothioconazole-desthio, prothioconazole	Prothioconazole-4-hydroxy, prothioconazole-*N*-glucuronide, prothioconazole-hydroxy-glucuronide, prothioconazole-4-hydroxy-glucuronide

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel Position	[Triazole-^{14}C]-Prothioconazole	
Milk	Thiocyanate	Prothioconazole, prothioconazole-hydroxy-glucuronide, prothioconazole-lactoside, prothioconazole-*S*-glucuronide/ prothioconazole-3-hydroxy-desthio, prothioconazole-4-hydroxy, prothioconazole-desthio
Liver	Prothioconazole, prothioconazole-4-hydroxy	Thiocyanate, prothioconazole-hydroxy-glucuronide, prothioconazole-hydroxy-sulfate/sulfate conjugate, prothioconazole-*S*-glucuronide/prothioconazole-3-hydroxy-desthio, prothioconazole-4-hydroxy-desthio, prothioconazole-*N*-glucuronide, prothioconazole-desthio, prothioconazole-*S*-methyl
Kidney	Prothioconazole, prothioconazole-*S*-glucuronide/prothioconazole-3-hydroxy-desthio	Thiocyanate, prothioconazole-4-hydroxy-glucuronide, prothioconazole-hydroxy-glucuronide, prothioconazole-*N*-glucuronide, prothioconazole-4-hydroxy, prothioconazole-desthio
Muscle	Thiocyanate, prothioconazole-*S*-glucuronide/prothioconazole-3-hydroxy-desthio	Prothioconazole, prothioconazole-4-hydroxy-glucuronide, prothioconazole-hydroxy-glucuronide, prothioconazole-*N*-glucuronide/prothioconazole-4-hydroxy, prothioconazole-desthio
Fat	Prothioconazole, thiocyanate, prothioconazole-hydroxy-glucuronide, prothioconazole-*S*-glucuronide/prothioconazole-3-hydroxy-desthio, prothioconazole-desthio	Prothioconazole-*N*-glucuronide/prothioconazole-4-hydroxy

STORAGE STABILITY OF PROTHIOCONAZOLE-DERIVED RESIDUES AND PROTHIOCONAZOLE-DESTHIO IN PLANT MATRICES

Storage stability studies were conducted on tomato, tomato paste, canola seed and oil, mustard green, turnip root, wheat bran, flour, forage, grain and straw. Samples were spiked individually with prothioconazole and prothioconazole-desthio. Data from these studies is being extended to the matrices listed below. Prothioconazole-derived residues and prothioconazole-desthio residues are stable for up to 1 year (interim report). The degree of loss of prothioconazole derived residues and prothioconazole-desthio residues is not expected to exceed 30% after 42 months.

Matrix	Temperature (°C)	Actual Storage Duration
Barley grain, hay, straw	-30.0 to -4.8	824–1269 days (27.1–41.7 months)
Bean, dried shelled	-24 to -22	490–536 days (16.1–17.6 months)
Canola seed, meal, refined oil	-30.0 to -4.8	867–1265 days (28.5–41.6 months)
Mustard greens	-30.0 to -4.8	1135–1263 days (37.3–41.5 months)
Pea, dried shelled	-24 to -22	494–542 days (16.2–17.8 months)
Peanut nutmeat, meal, refined oil, dry roasted peanuts and peanut butter, hay	-30.0 to -4.8	911–1214 days (31–39.9 months)
Rice, grain; rice polished grain, bran and hulls	-30.0 to -4.8	902–1240 days (30–40.8 months)
Turnip tops, roots	-30.0 to -4.8	1136–1243 days (37.3–40.8 months)
Wheat forage, grain, hay, straw, aspirated grain fractions, bran, germ, flour, shorts	-30.0 to -4.8	854–1285 days (28.1–42 months)

STORAGE STABILITY OF PROTHIOCONAZOLE-DERIVED RESIDUES, PROTHIOCONAZOLE-DESTHIO AND PROTHIOCONAZOLE-4-HYDROXY IN FAT MATRICES

Data to be generated to confirm the stability of the prothioconazole, prothioconazole-desthio and prothioconazole-4-hydroxy metabolites in fat for a duration of 45 days at the 1.4- and 4.7-fold feeding level.

Summary of Residues from the Crop Field Trials With Prothioconazole

Crop Matrix	Applic. Rate [kg a.i./ha]	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
BARLEY (proposed use = 0.400 kg a.i./ha/season, 30-day PHI)									
Total Prothioconazole-derived Residues									
Barley grain	0.321–0.348	30–71	49	< 0.02	0.158	0.151	0.022	0.04	0.041
Barley hay	0.321–0.348	12–16	49	0.317	6.59	5.95	1.22	1.72	1.39
Barley straw	0.321–0.348	30–71	50	< 0.05	1.871	1.65	0.304	0.554	0.51

Summary of Residues from the Crop Field Trials With Prothioconazole									
Crop Matrix	Applic. Rate [kg a.i./ha]	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
1,2,4–Triazole Residues									
Barley grain	0.321–0.348	30–71	50	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Barley hay	0.321–0.348	12–16	49	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Barley straw	0.321–0.348	30–71	50	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Triazole Conjugate Residues									
Barley grain	0.321–0.348	30–71	50	< 0.10	0.915	0.909	0.239	0.3	0.215
Barley hay	0.321–0.348	12–16	49	< 0.05	0.547	0.445	0.135	0.134	0.104
Barley straw	0.321–0.348	30–71	50	< 0.1	0.385	0.359	0.05	0.09	0.093
CANOLA (proposed use = 0.400 kg a.i./ha/season, 36-day PHI)									
Total Prothioconazole-derived Residues									
Canola seed	0.39–0.42	36–83	44	< 0.020	0.097	0.086	0.01	0.015	0.0169
1,2,4-Triazole Residues									
Canola seed	0.39–0.42	36–83	44	< 0.020	< 0.020	< 0.020	0.01	0.01	0
Triazole Conjugate Residues									
Canola seed	0.39–0.42	36–83	44	0.064	0.848	0.716	0.311	0.321	0.124
DRIED PEA AND BEAN (proposed use = 0.600 kg a.i./ha/season, 7-day PHI)									
Total Prothioconazole-derived Residues									
Pea, dried shelled	0.595–0.615	7–8	26	< 0.05	0.684	0.661	0.025	0.156	0.219
Bean, dried shelled	0.598–0.650	7–8	20	< 0.05	0.288	0.243	0.025	0.062	0.072
1,2,4-Triazole Residues									
Pea, dried shelled	0.595–0.615	7–8	26	< 0.01	0.011	0.01	0.005	0.005	0.001
Bean, dried shelled	0.598–0.650	7–8	20	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Triazole Conjugate Residues									
Pea, dried shelled	0.595–0.615	7–8	26	< 0.05	0.789	0.775	0.085	0.177	0.213
Bean, dried shelled	0.598–0.650	7–8	20	< 0.02	0.311	0.249	0.045	0.08	0.093
PEANUT (proposed use = 0.800 kg a.i./ha/season, 14-day PHI)									
Total Prothioconazole-derived Residues									
Peanut nutmeat	0.792–0.823	13–15	24	< 0.02	< 0.02	< 0.02	0.01	0.01	0
Peanut hay	0.792–0.823	13–15	24	0.989	4.458	3.63	2.657	2.612	0.884
1,2,4-Triazole Residues									
Peanut nutmeat	0.792–0.823	13–15	24	< 0.02	0.02	< 0.02	0.01	0.01	0
Peanut hay	0.792-0.823	13–15	24	< 0.02	< 0.02	< 0.02	0.01	0.01	0

Summary of Residues from the Crop Field Trials With Prothioconazole									
Crop Matrix	Applic. Rate [kg a.i./ha]	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Triazole Conjugate Residues									
Peanut nutmeat	0.792–0.823	13–15	24	0.162	3.903	3.39	0.827	1.158	1.127
Peanut hay	0.792–0.823	13–15	24	< 0.10	1.278	1.244	0.176	0.323	0.361
RICE (proposed use = 0.320 kg a.i./ha/season, 40-day PHI)									
Total Prothioconazole-derived Residues									
Rice, grain	0.38–0.41	40–67	32	< 0.02	0.222	0.191	0.01	0.031	0.048
Rice, straw	0.38–0.41	40–67	32	< 0.05	1.277	1.189	0.432	0.464	0.319
1,2,4–Triazole Residues									
Rice, grain	0.38–0.41	40–67	32	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Rice, straw	0.38–0.41	40–67	32	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Triazole Conjugate Residues									
Rice, grain	0.38–0.41	40–67	32	< 0.05	0.571	0.553	0.025	0.103	0.148
Rice, straw	0.38–0.41	40–67	32	< 0.05	0.506	0.478	0.025	0.088	0.122
WHEAT (proposed use = 0.400 kg a.i./ha/season, 30-day PHI)									
Total Prothioconazole-derived Residues									
Wheat hay	0.315–0.350	12–17	66	0.288	3.571	3.543	1.269	1.42	0.97
Wheat grain	0.315–0.350	10; 30–57	66	< 0.02	0.061	0.045	0.01	0.014	0.011
Wheat straw	0.315–0.350	10; 30–57	64	0.106	1.96	1.899	0.35	0.577	0.471
Wheat forage	0.320–0.336	7	46	0.061	6.987	5.842	1.352	1.401	1.268
1,2,4-Triazole Residues									
Wheat hay	0.315–0.350	12–17	66	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Wheat grain	0.315–0.350	10; 30–57	66	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Wheat straw	0.315–0.350	10; 30–57	66	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Wheat forage	0.320–0.336	7	46	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Triazole Conjugate Residues									
Wheat hay	0.315–0.350	12–17	66	0.018	0.665	0.631	0.204	0.22	0.124
Wheat grain	0.315–0.350	10; 30–57	66	0.098	1.76	1.76	0.46	0.534	0.32
Wheat straw	0.315–0.350	10; 30–57	64	< 0.025	0.495	0.449	0.063	0.095	0.104
Wheat forage	0.320–0.336	7	46	< 0.01	0.175	0.173	0.038	0.05	0.042

[1] HAFT = highest average field trial.
[2] In one field trial, the total application rate was 0.420 kg a.i./ha; we note that this trial did not include maximum residues for any of the metabolites.

Summary of Residue Data in Rotational Crops Following Primary Treatment With Prothioconazole									
Commodity	Applic. Rate [kg a.i./ha]	PBI (days)	Residue Levels (ppm)[1]						
			n	Min.	Max.	HAFT[2]	Median (STMdR[3])	Mean (STMR[4])	Std. Dev.
Total Prothioconazole-Derived Residues									
Mustard greens	0.81	31–34	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0
Turnip roots	0.81	31–34	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0

Summary of Residue Data in Rotational Crops Following Primary Treatment With Prothioconazole									
Commodity	Applic. Rate [kg a.i./ha]	PBI (days)	Residue Levels (ppm)[1]						
			n	Min.	Max.	HAFT[2]	Median (STMdR[3])	Mean (STMR[4])	Std. Dev.
Turnip tops	0.81	31–34	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0
Wheat forage	0.81	28–30	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0
Wheat hay	0.81	28–30	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0
Wheat grain	0.81	28–30	6	< 0.02	< 0.02	< 0.02	0.01	0.01	0
Wheat straw	0.81	28–30	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0
1*H*-1,2,4-Triazole Residues									
Mustard greens	0.81–0.82	31–34	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
		104–119	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Turnip roots	0.81	31–34	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0
		104–119	6	< 0.05	< 0.05	< 0.05	0.025	0.025	0
Turnip tops	0.81	31–34	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
		104–119	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Wheat forage	0.81	28–30	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
		119–120	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Wheat hay	0.81	28–30	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
		119–120	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Wheat grain	0.81	28–30	6	< 0.01	0.01	0.01	0.005	0.007	0.002
		119–120	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Wheat straw	0.81	28–30	6	< 0.01	0.01	0.01	0.005	0.007	0.002
		119–120	6	< 0.01	< 0.01	< 0.01	0.005	0.005	0
Triazole Conjugate Residues									
Mustard greens	0.81-0.82	31–34	6	0.102	0.313	0.311	0.253	0.222	0.097
		104–119	6	0.081	0.392	0.309	0.142	0.182	0.115
Turnip roots	0.81	31–34	6	0.301	0.567	0.533	0.366	0.405	0.105
		104–119	6	0.066	0.201	0.191	0.104	0.123	0.055
Turnip tops	0.81	31–34	6	0.263	0.484	0.449	0.331	0.355	0.08
		104–119	6	0.095	0.254	0.242	0.198	0.178	0.068
Wheat forage	0.81	28–30	6	0.08	1.174	1.114	0.304	0.499	0.488
		119–120	6	0.164	0.333	0.311	0.29	0.266	0.071
Wheat hay	0.81	28–30	6	0.303	2.025	1.942	0.923	1.067	0.731
		119–120	6	0.406	0.763	0.717	0.542	0.563	0.135
Wheat grain	0.81	28–30	6	0.71	3.465	3.42	2.224	2.139	1.188
		119–120	6	0.615	1.754	1.739	1.011	1.122	0.509

Summary of Residue Data in Rotational Crops Following Primary Treatment With Prothioconazole									
Commodity	Applic. Rate [kg a.i./ha]	PBI (days)	Residue Levels (ppm)[1]						
			n	Min.	Max.	HAFT[2]	Median (STMdR[3])	Mean (STMR[4])	Std. Dev.
Wheat straw	0.81	28–30	6	0.074	0.719	0.671	0.366	0.371	0.269
		119–120	6	0.103	0.278	0.27	0.189	0.19	0.072

[1] For the calculation of minimum, maximum and HAFT values, the LOQ value (< 0.01, < 0.02 or < 0.05 ppm) was used for residues reported as below the LOQ. For calculation of the median, mean and standard deviation, ½LOQ was used for residues reported as below the LOQ.
[2] HAFT = highest average field trial.
[3] STMdR = supervised trial median residue.
[4] STMR = supervised trial mean residue.

AVERAGE PROCESSING FACTORS FOR PROTHIOCONAZOLE-DERIVED RESIDUES				
Raw Agricultural Commodity	Processed Commodity	Total Prothioconazole-Derived Residues	1,2,4-Triazole	Triazole Conjugate Residues
Canola	Meal	< 0.7	NC	2.9
	Refined oil	< 0.7	NC	< 0.02
Peanut	Meal	> 7.9	> 1.9	1.9
	Refined oil	NC	NC	< 0.01
	Dry roasted peanuts	NC	> 12.5	0.5
	Peanut butter	NC	> 11.9	0.6
Rice	Polished grain	< 0.1	NC	0.5
	Bran	0.6	NC	6.9
	Hulls	4.4	NC	0.3
Wheat	Aspirated grain fractions	245	NC	0.3
	Bran	2.4	NC	3.1
	Flour	< 0.4	NC	0.5
	Germ	2	NC	3.6
	Middlings	0.6	NC	0.6
	Shorts	1	NC	1.5
NC = no concentration				

LIVESTOCK FEEDING			
Maximum theoretical dietary burdens are:12.97 ppm (beef); 20.86 ppm (dairy); 0.45 ppm (poultry) and 2.71 ppm (swine).			
Tissues/Matrices	Feeding Level	Mean Residue Levels (ppm)	Anticipated Residues (ppm)
Whole milk	29.5	0.0075	0.0053 ppm (based on MTDB of 20.86 ppm and an R/F ratio of 0.00025).
	98.4	0.0077	
Fat	9.9	0.075	0.158 ppm (based on MTDB of 20.86 ppm and an R/F ratio of 0.0075).
	29.5	0.075	
	98.4	0.087	
Kidney	9.9	0.073	0.156 ppm (based on MTDB of 20.86 ppm and the equation y = 0.0082x - 0.015)
	29.5	0.207	
	98.4	0.795	
Liver	9.9	0.099	0.1984 ppm (based on MTDB of 20.86 ppm and the equation y = 0077x + 0.0378)
	29.5	0.277	
	98.4	0.796	
Muscle	29.5	0.015	0.0106 ppm (based on the MTDB of 20.86 ppm and an R/F ratio of 0.00051).
	98.4	0.015	
PROPOSED MRLs (as per MRL calculator)			
Barley grain		0.35 ppm	
Canola, rapeseed, oriental mustard		0.15 ppm	
Chickpea, lentil		0.9 ppm	
Wheat grain		0.07 ppm	
Fat of cattle, sheep, horse, goat		0.1 ppm	
Milk; poultry liver; meat of cattle, sheep, horse, goat		0.02 ppm	
Hog meat byproducts		0.05 ppm	
Meat byproducts of cattle, sheep, horse, goat		0.2 ppm	

Table 2 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT **Primary Crops** **Rotational Crops**		Prothioconazole, prothioconazole-desthio	
METABOLIC PROFILE IN DIVERSE CROPS		Similar in three diverse crops (peanut, wheat, sugar beet)	
ANIMAL STUDIES—Poultry and Ruminant			
RESIDUE DEFINITION FOR ENFORCEMENT		Prothioconazole, prothioconazole-desthio and their conjugates	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Prothioconazole, prothioconazole-desthio and prothioconazole-4-hydroxy (and their conjugates)	
METABOLIC PROFILE IN ANIMALS		Quantitative and qualitative differences in poultry and ruminants, but does not affect overall profile assessment.	
FAT SOLUBLE RESIDUE		Yes	
DIETARY RISK From Food and Water			
Chronic Non-Cancer Dietary Risk **ADI = 0.004 mg/kg bw** **EEC = 25.1 µg/L (level 2)** **Refined includes STMRs, experimental processing factors and market values for peanuts and rice.**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Refined Food	**Refined Food + EEC**
	All infants < 1 year old	7.3	50.7
	Children 1 to 2 years	22	41.6
	Children 3 to 5 years	15.1	33.5
	Children 6 to 12 years	9.2	21.9
	Youth 13 to 19 years	4.6	14.2
	Adults 20 to 49 years	3.3	15.6
	Adults 50+ years	2.9	15.9
	Total population	5.1	18.3
Chronic Non-Cancer Dietary Risk **ADI = 0.002 mg/kg bw**	**Females 13+**	6.3	30.9
Acute Dietary Exposure Analysis, 95th percentile **EEC = 25.6 µg/L (level 2)**	**POPULATION**	**ESTIMATED RISK (% of ARfD)**	
		Refined Food	**Refined Food + EEC**
ARfD = 0.002 mg/kg bw	**Females 13+**	15.8	71.5

Appendix III Environmental Assessment

Table 1 Physical and Chemical Properties of Prothioconazole Relevant to the Environment

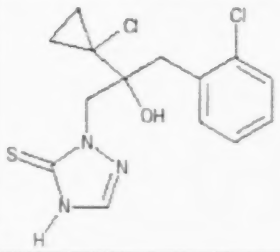
Property	Value	Comments
Chemical structure Prothioconazole (JAU6476) 2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione		CAS no.178928-70-6 Molecular weight: 344.264 g/mole Molecular formula: $C_{14}H_{15}C1_2N_3OS$
Water solubility (mg/L) at 20°C	**pH** **Solubility** 4 5 8 300 9 2000	Solubility in water is pH dependent. Low solubility at acidic pH and very soluble at basic pH
Vapour pressure	$<<4 \times 10^{-7}$ Pa ($<<3.00025 \times 10^{-9}$ mm Hg) at 20 and 25°C	This value indicates that volatility is not expected to be a major route of dissipation.
Henry's law constant	4.6×10^{-7} Pa × m^3/mol 4.5×10^{-12} atm × m^3/mol $1/H = 5.3 \times 10^{9}$	Reviewer calculated. Based on this value, prothioconazole is expected to be non-volatile from water or moist soil, according to the USEPA (1975).
Log K_{ow}	**pH** **log K_{ow}** Water 4.05 4 4.16 7 3.82 9 2.0	These values indicate a potential for bioaccumulation in biological tissue at pH ≤ 7.
pK_a	pK_a = 6.9	Predominates as an anion at neutral and basic pH.
UV–visible absorption	Maximum at λ = 275 nm No absorption at λ > 300 nm.	These data indicate a low potential for phototransformation under environmentally relevant conditions.

Table 2 Physical and Chemical Properties of Prothioconazole-desthio Relevant to the Environment

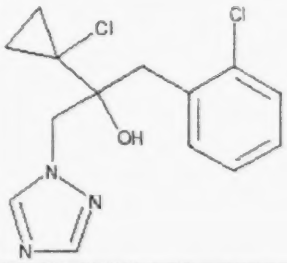
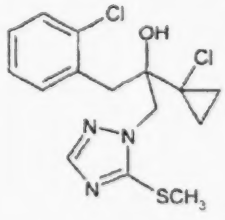
Property	Value	Comments
Chemical structure Prothioconazole-desthio 2-(1-Chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol		CAS No. 120983-64-4 Molecular weight: 312.3 g/mole Molecular formula: $C_{14}H_{15}C1_2N_3O$
Water solubility (mg/L) (at approximately 22°C)	**pH** **Solubility** 5 27.5 7 22.0 9 32.4 unbuffered 29.0	Data from hydrolysis study. Soluble
Vapour pressure	Not available	
Henry's law constant	Not available	
Log K_{ow}	3.04	The pH was not specified. This value indicates a potential for bioaccumulation in biological tissue.
pK_a	Not available	
UV–visible absorption	Maximum at λ = 197 nm No absorption at λ> 317 nm	These values indicate a low potential for phototransformation under environmentally relevant conditions.

Table 3 Physical and Chemical Properties of Prothioconazole-*S*-Methyl Relevant to the Environment

Property	Value	Comments
Chemical structure Prothioconazole-*S*-methyl (WAK7861) (alpha-1(1-chlorocyclopropyl)-alpha-[(2-chlorophenyl)methyl]-3-(methylthio)-1H-1,2,4-triazole-1-ethanol)		CAS No.178928-71-7 Molecular weight: 358.3 g/mole Molecular formula: $C_{15}H_{17}C1_2N_3OS$
Water solubility	Not available	
Vapour pressure	Not available	

Property	Value	Comments
Henry's law constant	Not available	
Log K_{ow}	4.19	The pH was not specified. This value indicates a potential for bioaccumulation in biological tissue.
pK_a	Not available	
UV–visible absorption	Not available	

Table 4 Physical and Chemical Properties of 1,2,4-triazole Relevant to the Environment

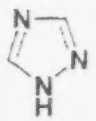
Property	Value	Comments
Chemical structure 1,2,4-Triazole 1*H*-1,2,4-triazole		CAS No. 288-88-0 Molecular weight: 69.1 g/mole Molecular formula: $C_2H_3N_3$

Table 5 Physical and Chemical Properties of Prothioconazole-thiazocine Relevant to the Environment

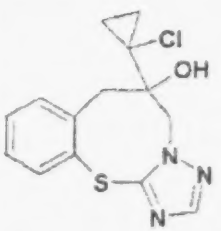
Property	Value	Comments
Chemical structure Prothioconazole-thiazocine 6-(1-chlorocyclopropyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[5,1-b][1,3]benzothiazocin-6-ol		CAS No. N/A Molecular weight: 307.8 g/mole Molecular formula: $C_{14}H_{14}ClN_3OS$

Table 6 Fate and Behaviour in the Terrestrial Environment

Property	Test Substance	Value	Comments
Abiotic Transformation			
Hydrolysis	Prothioconazole at pH 4, pH 7, pH 9 (25°C)	Stable	Hydrolysis is not a route of transformation. Extrapolated from data at 50°C
	Prothioconazole-desthio at pH 5, pH 7 and pH 9 (25°C)	Stable	Hydrolysis is not a route of transformation.
Phototransformation on soil	Prothioconazole and prothioconazole-desthio	Stable	Not an major route of transformation in the environment. Phototransformation half-life could not be calculated as dissipation was faster in dark samples than in irradiated samples.
Phototransformation in air	Prothioconazole	No data required	Not volatile
Biotransformation			
Biotransformation in aerobic soil	Prothioconazole	Total toxic residue DT_{50}: 3.6–95.2 days; DT_{90}: 332.3–1704.6 days	Non-persistent to moderately persistent in soil, according to Goring et al. (1975) DT_{90}s have a degree of uncertainty due to extrapolation beyond the time limits of the sampling period (120-day and 365-day study durations).
Biotransformation in anaerobic soil	No data provided		

Property	Test Substance	Value	Comments
Mobility			
Adsorption in soil	Prothioconazole	K_{oc} 1092–2802 mL/g, based on HPLC methods and modelling of physical-chemical properties	Slight to low mobility according to McCall et al. (1981)
	Prothioconazole-desthio	K_{oc} 418–549 mL/g	Low to moderate mobility according to McCall et al. (1981)
	Prothioconazole-*S*-methyl	K_{oc} 2234–3779 mL/g	Slight mobility according to McCall et al. (1981)
	Prothioconazole-thiazocine	K_{oc} 129 mL/g, based on HPLC methods	High mobility according to McCall et al. (1981)
	1,2,4-triazole	K_{oc} 68–251 mL/g	Moderate to high according to McCall et al. (1981)
Soil leaching	Prothioconazole	No residues detected beyond the top treated soil layer (0–6 cm) or in leachates. Prothioconazole-desthio: detected in first 12 cm Prothioconazole-*S*-methyl: only detected in 0–6 cm layer	Supplemental results due to low leachate volume Prothioconazole: low potential for leaching Prothioconazole-desthio and prothioconazole-*S*-methyl: slightly higher mobility than parent
	Aged residue	Very low total radioactive residues detected in the leachate (1.05%) and only 1.37% of parent was translocated below the aged soil layer Prothioconazole-desthio: Slight tendency to move downward, detected in aged layer and in the 0–6 and 6–12 cm layer Prothioconazole-*S*-methyl: Slight tendency to move downward, majority detected was in top two segments	Low potential for leaching Transformation products are slightly more mobile than the parent.
Volatilization	Prothioconazole	Vapour pressure: $<<4 \times 10^{-7}$ Pa at 20 and 25°C Henry's law constant: 4.5×10^{-12} atm × m³/mol $1/H = 5.3 \times 10^{9}$	Non-volatile; non-volatile from water or moist soil. Not an major route of transformation.

Property	Test Substance	Value	Comments
Field Studies			
Field dissipation	JAU6476 480 SC (Proline) a.i. prothioconazole	Total toxic residue DT_{50}: 8.2–111.6 days in Manitoba and Saskatchewan; Half-life of 296.3 days in New York DT_{90}: 756–1117 days in Manitoba and Saskatchewan $t_{9/10}$: 1027.9 days in New York	Total toxic residues are non-persistent to persistent under field conditions, according to Goring et al. (1975). Significant carryover of total toxic residues to the following growing season is not expected.
Field leaching	JAU6476 480 SC (Proline) a.i. prothioconazole	No residues of parent detected below 15 cm. Prothioconazole-desthio: No residues detected below 30 cm Prothioconazole-*S*-methyl: No residues detected below 15 cm 1,2,4-triazole: No residues detected below 45 cm	Low potential for leaching

Table 7 Transformation Products in the Terrestrial Environment

Fate Process	Test Material	Major Transformation Products (maximum concentration, % of applied material)	Minor Transformation Products (maximum concentration, % of applied material)
Hydrolysis	Prothioconazole	None	None
Phototransformation on soil	Prothioconazole	Prothioconazole-desthio (38.5%) (detected in both irradiated and dark samples; transformation attributed to biotransformation)	Prothioconazole-triazolinone (2.5%) Prothioconazole-sulfonic acid (3.0%) Unknowns 1, 2 and 3 (≤ 3.1%) Carbon dioxide (0.7%) All detected in both irradiated and dark samples except unknown 2, found in the dark samples only.
Biotransformation in aerobic soil	Prothioconazole	Prothioconazole-desthio (20.9–49.4%) Prothioconazole-*S*-methyl (3.8–14.6%)	Prothioconazole-triazolinone (≤ 3.1%) Prothioconazole-sulfonic acid (≤ 8.3%) 1,2,4-triazole (<2%) 2-chlorobenzoic acid (≤ 2.2%) Prothioconazole-6-OH-desthio (≤ 4.6%) Prothioconazole-3-OH-desthio (< 2%) Carbon dioxide (≤ 17.9%) Z2, Z4, Z17 and other unidentified transformation products: (each ≤ 4.1%)
	Prothioconazole-desthio	Carbon dioxide (29.2–60.8%)	M1, M2 and other unidentified transformation products: (each ≤ 7.9%)
	Prothioconazole-*S*-methyl	Carbon dioxide (4.8–51.1%) M2 (5.2–10%) M6 (6.1–24.7%)	M3, M4, M5, M7 and other transformation products: (each ≤ 7.6%)
Biotransformation in anaerobic soil (flooded soil)	Prothioconazole	No data provided	
Field dissipation	JAU6476 480 SC (Proline) a.i. prothioconazole	Sites: Saskatchewan, Manitoba, New York Prothioconazole-desthio (24.3-30.3%) 1,2,4-triazole (1.7–18.2%)	Prothioconazole-*S*-methyl (4.5–6.1%) Prothioconazole-thiazocine (1.2%)

Table 8 Fate and Behaviour in the Aquatic Environment

Property	Test Material	Value	Comments
Abiotic Transformation			
Hydrolysis	Prothioconazole pH 4, pH 7, pH 9 (25°C), extrapolated from data at 50°C	Stable	Hydrolysis is not a route of transformation.
	Prothioconazole-desthio at pH 5, pH 7 and pH 9 (25°C)	Stable	Hydrolysis is not a route of transformation.
Phototransformation in water	Prothioconazole	Prothioconazole + prothioconazole-desthio: 19.9 days (continuous irradiation), equivalent to a predicted environmental half-life of 101.9 days in June sunlight Prothioconazole alone: 1.9 days, equivalent to a predicted environmental half-life of 9.6–9.7 days	Assumed all transformation from phototransformation as the compound is stable to hydrolysis. Not a major route of transformation.
Biotransformation			
Biotransformation in aerobic water systems	Prothioconazole	Total toxic residue DT_{50}: 26.8–41.5 days; DT_{90}: 142.3–301.1 days	Slightly persistent, according to McEwen and Stephenson (1979)
Biotransformation in anaerobic water systems	Prothioconazole	Total toxic residue half-life: 1386.3 days; $t_{0.10}$: 4605.2 days	Persistent, according to McEwen and Stephenson (1979)
Field Studies			
Field dissipation	No data provided; not required.		

Table 9 Transformation Products in the Aquatic Environment

Fate Process	Test Material	Major Transformation Products (maximum concentration, % of applied prothioconazole)	Minor Transformation Products (maximum concentration, % of applied prothioconazole)
Hydrolysis	Prothioconazole	None	None
Phototransformation in water	Prothioconazole	Prothioconazole-desthio (54.8–55.7%) Prothioconazole-thiazocine (9.5–14.1%) 1,2,4-triazole (11.9%)	Met 2B, 3, 4, 5, 6, 7 (≤ 7.0%) Up to 9 unassigned
Biotransformation in aerobic water/sediment systems	Prothioconazole	Prothioconazole-desthio (32.3% water; 26.9% sediment 1,2,4-triazole (37.2% water) Prothioconazole-*S*-methyl (9.6% sediment, 12.7% system) Carbon dioxide (2.0–29%)	Prothioconazole-*S*-methyl (3.1% water) 1,2,4-triazole (6.1% sediment) Prothioconazole-triazolinone (2.2% water, 6.1% sediment) Prothioconazole-triazolylketone (8.0% water, 5.8% sediment)
Biotransformation in anaerobic water/sediment systems	Prothioconazole	Prothioconazole-*S*-methyl (77.0% sediment)	Prothioconazole-*S*-methyl (8.6% water) Z4 (3.25% water), Z5 (2.56% water)
Field dissipation	Prothioconazole	No data provided	

Table 10 Major Groundwater and Surface Water Model Inputs for Level 1 Assessment of Prothioconazole and Its Transformation Products Prothioconazole-desthio and Prothioconazole-*S*-Methyl

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Canola, wheat, chickpeas, lentils, barley
	Maximum allowable application rate per year (kg a.i./ha)	0.6
	Maximum rate each application (kg a.i./ha)	0.2
	Maximum number of applications per year	3
	Minimum interval between applications (days)	7–10 days, depending on crop
	Method of application	Ground (also aerial for canola)

Type of Input	Parameter	Value
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Phototransformation half-life in water (days)	19.9
	Adsorption K_{oc} (mL/g)	418
	Aerobic soil biotransformation half-life (days)	552.3
	Aerobic aquatic biotransformation half-life (days)	90.7
	Anaerobic aquatic biotransformation half-life (days)	1386.3

Table 11 Level 1 Aquatic Ecoscenario Modelling Results for Prothioconazole, Prothioconazole-desthio and Prothioconazole-*S*-Methyl Combined

Region	Date	Total Toxic Residue EEC (mg/L)					
		Peak	96-hour	21-day	60-day	90-day	Yearly
Pacific	22 July	0.0103	0.0097	0.008	0.0065	0.0063	0.0053
Prairies	15 May	0.0209	0.0197	0.0167	0.0142	0.0132	0.0091
Ontario	10 July	0.0147	0.0139	0.0121	0.0109	0.0107	0.0092
Quebec	12 June	0.0122	0.0118	0.011	0.0106	0.0104	0.0089
Atlantic	13 July	0.0156	0.0147	0.0125	0.0113	0.0107	0.0084

Table 12 Level 1 Estimated Environmental Concentrations of Prothioconazole and Its Transformation Products Prothioconazole-desthio and Prothioconazole-*S*-Methyl Combined in Potential Drinking Water Sources

Crop (annual application rate)	Groundwater EEC (µg/L)		Surface Water EEC (µg/L)			
			Reservoir		Dugout	
	Acute[1]	Chronic[2]	Acute[3]	Chronic[4]	Acute[3]	Chronic[4]
Chickpea (0.2 kg a.i./ha × 3)	49.9	49.6	28.8	5.1	34	22.8

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peak concentrations
4 90th percentile of yearly average concentrations

Table 13 Level 2 Estimated Environmental Concentrations of Prothioconazole and Its Transformation Products Prothioconazole-desthio and Prothioconazole-*S*-methyl Combined in Potential Drinking Water Sources

Crop (annual application rate)	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Chickpeas (0.2 kg a.i./ha × 3) (surface water) Barley/wheat (0.2 kg a.i./ha × 2) (groundwater)	25.6	25.1	16.5	6.7	24.7	14.8

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peak concentrations
4 90th percentile of yearly average concentrations

Table 14 Maximum Total Toxic Residue EEC in Vegetation and Insects After a Direct Overspray

Matrix	Total Toxic Residue EEC (mg/kg fw)[a]	Fresh-to-Dry Weight Ratios	Total Toxic Residue EEC (mg/kg dw)
Short range grass	62.5	3.3[b]	206.3
Leaves and leafy crops	32.7	11.0[b]	359.9
Long grass	28.6	4.4[b]	126.0
Forage crops	35.0	5.4[b]	189.3
Small insects	15.2	3.8[c]	57.7
Pods with seeds	3.1	3.9[c]	12.2
Large insects	2.6	3.8[c]	9.9
Grain and seeds	2.6	3.8[c]	9.9
Fruit	3.9	7.6[c]	29.7

a Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
b Fresh-to-dry weight ratios from Harris (1975)
c Fresh-to-dry weight ratios from Spector (1956)

Table 15 Maximum Total Toxic Residue EEC in Diets of Birds and Mammals

Organism	Matrix	Total Toxic Residue EEC (mg/kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	51.1
Mallard duck	30% large insects 70% grain	9.9
Rat	70% short grass 20% grain/seeds 10% large insects	147.4
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	146.5
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	220.4

Table 16 Effects on Terrestrial Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Invertebrates				
Earthworm (*Eisenia fetida*)	14-day Acute	Prothioconazole (98.3%)	NOEC: 562 mg a.i./kg dw soil LC_{50}: > 1000 mg a.i./kg dw soil	Non-lethal at highest test concentration 1000 mg a.i./kg dw soil Effects: weight loss
	14-day Acute	Prothioconazole-desthio (97.6%)	NOEC: 100 mg/kg dw soil LC_{50}: > 1000 mg/kg dw soil	Non-lethal at highest test concentration 1000 mg/kg dw soil Effects: weight loss
	14-day Acute	Prothioconazole-*S*-methyl (99.1%)	NOEC: 100 mg/kg dw soil LC_{50}: > 1000 mg/kg dw soil	Non-lethal at highest test concentration 1000 mg/kg dw soil Effects: weight loss
	14-day Acute	JAU6476 SC 480 (EP) (478.2 g a.i./L)	NOEC: 1000 mg EP/kg dw soil LC_{50}: > 1000 mg EP/kg dw soil	Non-lethal at highest test concentration 1000 mg EP/kg dw soil Effects: none

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
	56-day Chronic (28-day exposure)	Prothioconazole-desthio (96.9%)	NOEC (adult mortality and weight): 32 mg/kg dw soil, highest dose tested NOEC (reproduction): 1.0 mg/kg dw soil	No classification Effects: number of offspring/surviving adult, no dose-response relationship observed for weight
	56-day Chronic (28-day exposure)	Prothioconazole-*S*-methyl (99.1%)	NOEC (weight): 100 mg/kg dw soil NOEC (reproduction): 316 mg/kg dw soil	No classification Effects: weight loss, number of offspring/surviving adult
	56-day Chronic (28-day exposure)	JAU6476 EC 250 (249.24 g a.i./L)	NOEC: 1000 g a.i./ha, highest concentration tested	No classification Effects: none
Earthworm populations	11 months (3 applications at 200 g a.i./ha at 2- to 3-week intervals)	JAU6476 EC 250 (EP) (249.7 g a.i./L)	NOEC: 600 g a.i./ha, highest concentration tested	No classification Effects: no effect on populations
Honeybee (*Apis mellifera*)	48-hour Acute Oral	Prothioconazole (98.6%)	NOEL: 71 µg a.i./bee LD_{50}: > 71 µg a.i./bee	Relatively non-toxic Effects: none
	48-hour Acute Contact	Prothioconazole (98.6%)	NOEL: 200 µg a.i./bee LD_{50}: > 200 µg a.i./bee	Relatively non-toxic Effects: mortality at all levels but no dose-response relationship
	48-hour Acute Oral	JAU6476 SC 480 (EP) (478.2 g a.i./L)	NOEL: 232 µg EP/bee, equivalent to 95.1 µg a.i./bee LD_{50}: > 232 µg EP/bee, equivalent to > 95.1 µg a.i./bee	Relatively non-toxic Effects: none
	48-hour Acute Contact	JAU6476 SC 480 (EP) (478.2 g a.i./L)	NOEL: 200 µg EP/bee, equivalent to 82 µg a.i./bee LD_{50}: > 200 µg EP/bee, equivalent to > 82 µg a.i./bee	Relatively non-toxic Effects: none

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Predatory arthropod Predaceous mite (*Hypoaspis aculeifer*)	34-day Life Cycle	Prothioconazole (96.1%)	NOER: 225 000 g a.i./ha (100 mg a.i./kg soil), highest concentration tested. LR_{50}: > 100 mg a.i./kg soil (225 000 g a.i./ha) Reduction in beneficial capacity: 14.4% at 225 000 g a.i./ha	Harmless up to 100 mg a.i./kg soil (225 000 g a.i./ha) Effects: no mortality; no statistically significant effects on reproduction
Predatory arthropod Predaceous mite (*Typhlodromus pyri*)	14-day Contact	JAU6476 480 SC (EP) (478.2 g a.i./L)	NOER: 600 g a.i./ha (mortality) NOER: 380 g a.i./ha (reproduction) LR_{50}: > 600 g a.i./ha Reduction in beneficial capacity: 41.6% at 600 g a.i./ha	Harmless up to 380 g a.i./ha; slightly harmful at 600 g a.i./ha Effects: reduced number of eggs/female (not statistically significant)
Parasitic arthropod Parasitic wasp (*Aphidius rhopalosiphi*)	14-day Contact	JAU6476 480 SC (EP) (478.2 g a.i./L)	NOER: 600 g a.i./ha LR_{50}: > 600 g a.i./ha No reduction in beneficial capacity up to 600 g a.i./ha	Harmless up to 600 g a.i./ha Effects: none

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Terrestrial arthropods Springtail (*Folsomia candida*)	Chronic Contact 28 days	Prothioconazole (95.9%)	NOER: 64 mg a.i./kg soil (mortality and reproduction), highest concentration tested LR_{50}: > 64 mg a.i./kg soil	Non-lethal at highest test concentration 64 mg a.i./kg soil Effects: no dose response relationship observed
	Chronic Contact 28 days	Prothioconazole-desthio (96.4%)	NOER: 62.5 mg/kg soil (reproduction) LR_{50}: > 1000 mg/kg soil	Non-lethal at highest test concentration 1000 mg/kg soil Effects: number of offspring
	Chronic Contact 28 days	Prothioconazole-*S*-methyl (98.8%)	NOER: 31.6 mg/kg soil (mortality and reproduction), highest concentration tested LR_{50}: > 31.6 mg/kg soil	Non-lethal at highest test concentration 31.6 mg/kg soil Effects: no dose-response relationship observed
Birds				
Bobwhite quail (*Colinus virginianus*)	Acute Oral single dose; birds observed for 14 days	Prothioconazole (98.4%)	NOEL: 2000 mg a.i./kg bw (mortality) NOEL: 200 mg a.i./kg bw (diarrhea) LD_{50}: > 2000 mg a.i./kg bw	Practically non-toxic Effects: sublethal effects
	Acute Oral single dose; birds observed for 14 days	prothioconazole-desthio (93.7%)	NOEL: 1000 mg/kg bw (mortality) NOEL: 500 mg/kg bw (clinical signs of toxicity, weight reduction) LD_{50}: > 2000 mg/kg bw	Practically non-toxic Effects: mortality, clinical signs of toxicity, weight reduction, reduced feed consumption
	Dietary 5-day exposure, 3-day postexposure	Prothioconazole (98.4%)	NOEC: 4983 mg a.i./kg diet (mortality) NOEC: 622 mg a.i./kg diet (necropsy findings) LC_{50}: > 4983 mg a.i./kg diet	Practically non-toxic Effects: intestinal inflammation

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
	Dietary 5-day exposure, 3-day postexposure	Prothioconazole-desthio (96.8%)	NOEC: 1243 mg/kg diet LC_{50}: 4252 mg/kg diet (3161–6501 mg/kg diet)	Slightly toxic Effects: mortality, clinical signs of toxicity, weight loss, reduced food consumption
	Reproduction 1-generation 21-week dietary	Pprothioconazole (98.7%)	Parental and reproductive NOEC: 982 mg a.i./kg diet	No classification Effects: none
	Reproduction 1-generation 22-week dietary	Prothioconazole-desthio (97.6%/96.8%)	Parental and reproductive: NOEC: 506.7 mg/kg diet	No classification Effects: none
Mallard duck (*Anas platyrhynchos*)	Dietary 5-day exposure, 3-day postexposure	Prothioconazole (98.7%)	NOEC: 5567 mg a.i./kg diet LC_{50}: > 5567 mg a.i./kg diet	Practically non-toxic Effects: none
	Reproduction 1-generation 21-week dietary	Prothioconazole (98.7% / 96.1%)	Parental and Reproductive: NOEC: 1978 mg a.i./kg diet	No classification Effects: none
	Reproduction 1-generation 20-week dietary	Prothioconazole-desthio (96.4%)	Parental and Reproductive: NOEC: 449 mg/kg diet	No classification Effects: none

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Mammals				
Rat (*Rattus norvegicus*)	Acute oral single dose	Prothioconazole (99.8%)	NOEL: 6200 mg a.i./kg bw (mortality) LD_{50}: ≥ 6200 mg a.i./kg bw	Practically non-toxic Effects: no mortality
	Acute oral single dose	Prothioconazole-desthio (93.7%)	NOEL: 1000 mg/kg bw (mortality) LD_{50}: 2506 mg/kg bw (females) LD_{50}: 2806 mg/kg bw (males)	Practically non-toxic Effects: mortality
	Acute oral single dose	Prothioconazole-*S*-methyl (98.3%)	NOEL: 2000 mg/kg bw (mortality) LD_{50}: > 2000 mg/kg bw	Practically non-toxic Effects: no mortality
	Acute oral single dose	JAU6476 480 SC (EP) (40.6%)	NOEL: 2000 mg/kg bw (mortality) LD_{50}: between 2000 and 5000 mg EP/kg bw	Practically non-toxic Effects: mortality only at highest dose
	Reproduction 2-generation gavage	Prothioconazole	NOEL: 100 mg a.i./kg bw/day, equivalent to an NOEC of 583.3 mg a.i./kg diet	Practically non-toxic Effects: reduced body weight and body-weight gain in parents, F_1 adults and pups of both generations; effects on estrous cycles
	Reproduction 2-generation gavage	Prothioconazole-desthio	NOEL (reproduction): 9.5 mg/kg bw/day, equivalent to an NOEC of 160 mg/kg diet	No classification
	Reproduction and developmental toxicity	Prothioconazole (percentage not specified)	NOEL (maternal and developmental for environmentally relevant endpoints): 80 mg/kg bw/day, equivalent to an NOEC of 467 mg/kg diet	No classification

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
	Developmental neurotoxicity	Prothioconazole-desthio (percentage not specified)	NOEL (maternal and developmental): 3.6 mg/kg bw/day, equivalent to an NOEC of 40 mg/kg diet	No classification
Mouse	Acute oral single dose	Prothioconazole-desthio (94.7%)	NOEL: 500 mg/kg bw (mortality) LD_{50}: 3459 mg/kg bw (females) LD_{50}: 2235 mg/kg bw (males)	Practically non-toxic Effects: mortality
Rabbit	Reproduction and development	Prothioconazole-desthio (percentage not specified)	NOEL (maternal): 10 mg/kg bw/day, equivalent to an NOEC of 333 mg/kg diet NOEL (developmental): 2 mg/kg bw/day, equivalent to an NOEC of 66.7 mg/kg diet	No classification
Vascular Plants				
Vascular plant Most sensitive: Dicot, cucumber (*Cucumis sativa*, Cucurbitaceae)	Seedling emergence Soil with planted seeds was sprayed 21-days postspray	JAU6476 480 SC (EP) (Guarantee: 414 g a.i./L)	Dicot, cucumber: EC_{25} (shoot height and dry weight): ≥ 305 g a.i./ha NOEC: 305 g a.i./ha	No classification Effects: reduced-shoot height and dry weight
	Vegetative vigour	JAU6476 480 SC (EP) (Guarantee: 414 g a.i./L)	EC_{25} (all species, all endpoints): > 305 g a.i./ha NOEC: 305 g a.i./ha	No classification Effects: none

[a] Atkins et al. (1981) for bees, Hassan et al. (1994) for predators and parasites, and the USEPA classification for others, where applicable (1985a, 1985b, 1985c).

Table 17 Effects of Prothioconazole, Prothioconazole-desthio, Prothioconazole-*S*-methyl and the Formulation JAU6476 480 SC on Aquatic Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Freshwater Species				
Daphnia magna	48-hour Acute static	Prothioconazole (98.4%)	NOEC: 0.93 mg a.i./L EC_{50}: 1.20 (1.09 to 1.32) mg a.i./L	Moderately toxic Effects: mortality/ immobilization
	48-hour Acute static	Prothioconazole-desthio (93.7%)	NOEC: 5.5 mg/L EC_{50}: between 5.5 and 10 mg/L	Moderately toxic Effects: mortality, sublethal effects
	48-hour Acute static	Prothioconazole-*S*-methyl (98.6%)	NOEC: 0.7 mg/L EC_{50}: 2.8 (2.2–4.3) mg/L	Moderately toxic Effects: mortality, sublethal effects
	48-hour Acute static-renewal	JAU6476 480 SC (EP) (41.1%)	NOEC: 0.81 mg a.i./L EC_{50}: 4.1 (2.2–5.47) mg a.i./L	Moderately toxic Effects: sublethal effects
	21-day Chronic static-renewal	Prothioconazole (98.8%)	NOEC (adult growth and reproduction): 0.51 mg a.i./L LC_{50}: 1.57 (1.24–2.05) mg a.i./L	No classification Effects: mortality, adult growth, reproductive effects
	21-day Chronic static-renewal	Prothioconazole-desthio (96.5%)	NOEC (mortality, growth): 0.83 mg/L LC_{50}: > 0.83 mg/L	No classification Effects: mortality, growth, reproduction
Midge (*Chironomus riparius*)	28-day Chronic static water-spiked exposure	Prothioconazole-desthio (97.6%)	NOEC: between 0.23 and 2.37 mg/L in overlying water EC_{50}: between 2.37 and 8.93 mg/L in overlying water	No classification Effects: emergence, development time, development rate Study of limited utility as some concentrations were not analytically verified at study initiation and termination.
Crayfish (*Procambarus clarkii*)	96-hour Acute static-renewal	Prothioconazole-desthio (98.5%)	LC_{50}: > 26 mg/L	Study of limited value due to excessive control mortality and molting. No apparent treatment-related effects.

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Rainbow trout (*Oncorhynchus mykiss*)	96-hour Acute static	Prothioconazole (98.4%)	NOEC: 0.99 mg a.i./L LC_{50}: 1.83 (0.99–3.08) mg a.i./L	Moderately toxic Effects: mortality, sublethal effects
	96-hour Acute static	Prothioconazole-desthio (93.7%)	NOEC (sublethal effects): 2.22 mg/L LC_{50}: 5.94 (4.20–8.40) mg/L	Moderately toxic Effects: mortality, sublethal effects
	96-hour Acute static-renewal	Prothioconazole-*S*-methyl (98.6%)	NOEC (sublethal effects): 0.265 mg/L LC_{50}: 1.78 (1.14–2.39) mg/L	Moderately toxic Effects: mortality, sublethal effects
	96-hour Acute static	JAU6476 480 SC (EP) (41.4%)	NOEC: 1.29 mg a.i./L LC_{50} : 1.69 (1.29–2.56) mg a.i./L	Moderately toxic Effects: mortality; sublethal effects
Bluegill sunfish (*Lepomis macrochirus*)	96-hour Acute static	Pprothioconazole (98.4%)	NOEC: 1.69 mg a.i./L LC_{50}: 4.59 (4.02–5.09) mg a.i./L	Moderately toxic Effects: mortality, sublethal effects
	96-hour Acute static-renewal	JAU6476 480 SC (EP) (43%)	NOEC: 2.81 mg a.i./L LC_{50}: 5.53 (2.81–> 5.80) mg a.i./L	Moderately toxic Effects: mortality, sublethal effects
Common carp (*Cyprinus carpio*)	96-hour Acute static	Prothioconazole (98.6%)	NOEC (sublethal effects): 0.91 mg a.i./L LC_{50}: 6.42 (4.79–8.91) mg a.i./L	Moderately toxic Effects: mortality, sublethal effects

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Fathead minnow (*Pimephales promelas*)	96-hour Acute static-renewal	Prothioconazole-desthio (96.5%)	NOEC (sublethal effects): 3.85 mg/L LC_{50}: 11.41 (7.99–16.30) mg/L	Slightly toxic Effects: mortality, sublethal effects
	Life cycle (approximately 9 month exposure) flow-through	Prothioconazole-desthio (96.4%)	NOEC: 0.148 mg/L	No classification NOEC based on effects on first-generation larval/juvenile survival, juvenile (8-weeks posthatch) and male growth, spawning frequency and morphological deformities
Freshwater alga Green algae (*Selenastrum capricornutum*)	Acute 96-hour static	Prothioconazole (98.3%)	NOEC: 0.371 mg a.i./L EC_{50} (cell density): 0.88 (0.78–1.0) mg a.i./L	No classification Effects: cell density, biomass, growth rate
	Acute 96-hour static	Prothioconazole-*S*-methyl (98.6%)	NOEC: < 1.03 mg/L EC_{50} (cell density): 2.8 (1.8–4.2) mg/L	No classification Effects: cell density, biomass, growth rate.
	Acute 96-hour static	JAU6476 480 SC (EP)	NOEC: 0.48 mg a.i./L EC_{50} (biomass): 0.92 (0.83–1.0) mg a.i./L	No classification Effects: cell density, biomass, growth rate
Freshwater alga Blue-green algae (*Anabaena flos-aquae*)	Acute 96-hour static	Prothioconazole (98.2%)	NOEC (cell density) 0.82 mg a.i./L EC_{50} (cell density): 3.5 (2.6–4.6) mg a.i./L	No classification Effects: cell density, biomass, growth rate
Freshwater alga Diatom (*Navicula pelliculosa*)	Acute 96-hour static	Prothioconazole (97.5%)	NOEC (cell density and biomass): < 0.0124 mg a.i./L, EC_{50}(biomass): 0.122 (0.108–0.137) mg a.i./L	No classification Effects: cell density, biomass, growth rate
Freshwater alga Green algae (*Scenedesmus subspicatus*)	Acute 96-hour static	Prothioconazole-desthio (93.7%)	NOEC: 0.050 mg/L EC_{50}(cell density): 0.074 (0.045–0.12) mg/L	No classification Effects: cell density, biomass, growth rate

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Vascular plant (*Lemna gibba*)	Dissolved 7-day static	Prothioconazole (98.2%)	NOEC (frond number and biomass): 0.00334 mg a.i./L EC_{50}: 0.0671 (0.0586–0.074) mg a.i./L, for frond numbers	No classification Effects: frond numbers, dry weight, biomass, growth rate
	Dissolved 7-day static	Prothioconazole-desthio (97%)	NOEC: 0.0058 mg/L EC_{50}: 0.0308 (0.0278–0.0333) mg/L for dry weight	No classification Effects: frond numbers, dry weight, biomass, growth rate
	Dissolved 7-day static	JAU6476 480 SC (EP) (42.1%)	NOEC: 0.0075 mg a.i./L EC_{50}: 0.0711 (0.0666–0.0744) mg a.i./L for frond numbers	No classification Effects: frond numbers, dry weight, biomass, growth rate
Marine Species				
Crustacean saltwater mysid (*Mysidopsis bahia*)	96-hour Acute flow-through	Prothioconazole (98.4%)	NOEC:0.99 mg a.i./L LC_{50}: 2.4 (2.0–4.1) mg a.i./L	Moderately toxic Effects: mortality, sublethal effects
	96-hour Acute flow-through	Prothioconazole-desthio (96.5%)	NOEC:0.026 mg/L LC_{50}: 0.060 (0.046–0.079) mg/L	Very highly toxic Effects: mortality, sublethal effects
	Chronic	Prothioconazole-desthio (97%)	NOEC (reproductive success): 0.064 mg/L	No classification Effects: reproduction
Mollusk Eastern oyster (*Crassostrea virginica*)	96-hour Acute flow-through (shell-deposition)	Prothioconazole (98.4%)	NOEC (reduced shell deposition): 0.76 mg a.i./L EC_{50}: 3.0 (2.6–3.5) mg a.i./L	Moderately toxic Effects: reduced shell deposition
Marine fish Sheepshead minnow (*Cyprinodon variegatus*)	96-hour Acute static-renewal	Prothioconazole (Purity 97.8%)	NOEC: 10.3 mg a.i./L, highest concentration tested LC_{50}: > 10.3 mg a.i./L	Practically non-toxic at the limit of solubility Effects: None
Marine alga Saltwater diatom (*Skeletonema costatum*)	96-hour Acute static	Prothioconazole (98.2%)	NOEC (cell density and biomass): 0.00448 mg a.i./L EC_{50}(growth rate): 0.0157 (0.0135–0.0178) mg a.i./L	No classification Effects: cell density, biomass, growth rate

[a] USEPA classification (1985d, 1985e, 1985f, 1985g, 1985h), where applicable

Table 18 Risk Classification Scheme

Risk Quotient (RQ) [EEC/NOEC or EEC/EC_{25} for terrestrial plants]	Risk Category
< 0.1	Negligible risk
0.1 – < 1.0	Low risk
1.0 – < 10	Moderate risk
10 – < 100	High risk
100 – < 1000	Very high risk
≥ 1000	Extremely high risk

Table 19 Risk to Terrestrial Organisms

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Risk
Invertebrates					
Earthworm	Acute: prothioconazole	NOEC: 562 mg a.i./kg dw soil	0.265 mg/kg soil	0.0005	Negligible
	Acute: prothioconazole-desthio	NOEC: 100 mg/kg dw soil	0.265 mg/kg soil	0.0026	Negligible
	Acute: prothioconazole-*S*-methyl	NOEC: 100 mg /kg dw soil	0.265 mg/kg soil	0.0026	Negligible
	Acute: JAU6476 480 SC (EP)	NOEC: 1000 mg EP/kg dw soil	0.646 mg EP/kg soil	0.001	Negligible
	Reproduction: prothioconazole-desthio	NOEC: 1 mg/kg dw soil	0.265 mg/kg soil	0.265	Low
	Reproduction: prothioconazole-*S*-methyl	NOEC: 100 mg/kg dw soil (weight reduction)	0.265 mg/kg soil	0.0026	Negligible
	Reproduction: JAU6476 EC 250	NOEC: 1000 g a.i./ha	595.5 g a.i./ha	N/A	Negligible
	Reproduction JAU6476 EC 250 (11 months)	NOEC: 600 g a.i./ha	595.5 g a.i./ha	N/A	Negligible
Bee	Oral: prothioconazole	LD_{50}: > 71 µg a.i./bee	201 g a.i./ha Cumulative application: 292.2 g a.i./ha	N/A	Relatively non-toxic based on Atkins et al. (1981)

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Risk
	Oral: JAU6476 480 SC (EP)	LD_{50}: > 232 µg EP/bee (equivalent to > 95.1 µg a.i./bee)	201 g a.i./ha Cumulative application: 292.2 g a.i./ha	N/A	Relatively non-toxic based on Atkins et al. (1981)
	Contact: prothioconazole	LD_{50}: > 200 µg a.i./bee	201 g a.i./ha Cumulative application: 292.2 g a.i./ha	N/A	Relatively non-toxic based on Atkins et al. (1981)
	Contact: JAU6476 480 SC (EP)	LD_{50}: > 200 µg a.i./bee, equivalent to 82 µg a.i./bee	201 g a.i./ha Cumulative application: 292.2 g a.i./ha	N/A	Relatively non-toxic based on Atkins et al. (1981)
Predatory mite	Contact: prothioconazole	NOER: 225 000 g a.i./ha equivalent to 100 mg a.i./kg soil	201 g a.i./ha Cumulative application: 292.2 g a.i./ha Equivalent to 0.265 mg/kg soil	N/A	Harmless according to Hassan et al. (1994)
	Contact: JAU6476 480 SC (EP)	NOER (mortality): 600 g a.i./ha NOER (reproduction): 380 g a.i./ha	201 g a.i./ha Cumulative application: 292.2 g a.i./ha	N/A	Harmless according to Hassan et al. (1994)
Parasitic wasp	Contact: JAU6476 480 SC (EP)	NOER: 600 mg a.i./kg soil	201 g a.i./ha Cumulative application: 292.2 g a.i./ha	N/A	Harmless according to Hassan et al. (1994)

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Risk
Terrestrial arthropod (springtail)	Reproduction: prothioconazole	NOEC: 64 mg a.i./kg dw soil	0.265 mg a.i./kg soil	0.0041	Negligible
	Reproduction: prothioconazole-desthio	NOEC: 1000 mg/kg dw soil (mortality) NOEC: 62.5 mg/kg dw soil (reproduction)	0.265 mg/kg soil	0.000265 0.0042	Negligible
	Reproduction: prothioconazole-*S*-methyl	NOEC: 31.6 mg/kg dw soil	0.265 mg/kg soil	0.0084	Negligible
Birds					
Bobwhite quail	Acute: prothioconazole	LD_{50}: > 2000 mg a.i./kg bw NOEL: 2000 mg a.i./kg bw (mortality) NOEL: 200 mg a.i./kg bw (diarrhea)	51.1 mg a.i./kg dw diet	> 546 days 546 days 54.6 days	Negligible
	Acute: prothioconazole-desthio	LD_{50}: > 2000 mg/kg bw NOEL: 1000 mg/kg bw (mortality) NOEL: 500 mg/kg bw (clinical signs of toxicity, weight reduction)	51.1 mg/kg dw diet	> 312 days 156 days 78.1 days	Negligible
	Dietary: prothioconazole	LC_{50}: > 4983 mg a.i./kg diet NOEC: 4983 mg a.i./kg diet (mortality) NOEC: 622 mg a.i./kg diet (necropsy findings)	51.1 mg a.i./kg dw diet	< 0.0103 0.0103 0.0822	Negligible
	Dietary: prothioconazole-desthio	LC_{50}: > 4252 mg/kg diet NOEC: 1243 mg/kg diet	51.1 mg/kg dw diet	< 0.012 0.0411	Negligible

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Risk
	Reproduction: prothioconazole	NOEC: 982 mg a.i./kg diet	51.1 mg a.i./kg dw diet	0.052	Negligible
	Reproduction: prothioconazole-desthio	NOEC: 506.7 mg a.i./kg diet	51.1 mg/kg dw diet	0.101	Negligible
Mallard duck	Dietary: prothioconazole	LC_{50}: > 5567 mg a.i./kg diet NOEC: 5567 mg a.i./kg diet	9.9 mg a.i./kg dw diet	< 0.00178 0.00178	Negligible
	Reproduction: prothioconazole	NOEC: 1978 mg a.i./kg diet	9.9 mg a.i./kg dw diet	0.005	Negligible
	Reproduction: prothioconazole-desthio	NOEC: 449 mg a.i./kg diet	9.9 mg/kg dw diet	0.022	Negligible
Mammals					
Rat	Acute: prothioconazole	LD_{50}: > 6200 mg a.i./kg bw NOEL: 6200 mg a.i. /kg bw (mortality)	147.4 mg a.i./kg dw diet	> 245 days 245 days	Negligible
	Acute: prothioconazole-desthio	LD_{50}: 2506 mg a.i./kg bw (females) NOEL: 1000 mg/kg bw (mortality)	147.4 mg/kg dw diet	99.2 days 39.6 days	Negligible
	Acute: prothioconazole-*S*-methyl	LD_{50}: > 2000 mg/kg bw NOEL: 2000 mg a.i. /kg bw (mortality)	147.4 mg/kg dw diet	> 79.2 days 79.2 days	Negligible
	Acute: JAU6476 480 SC (EP) (40.6%)	LD_{50}: between 812 and 2030 mg a.i./kg bw NOEL: 812 mg a.i./kg bw (mortality)	147.4 mg a.i./kg dw diet	Between 32.1 and 80.4 days 32.1 days	Negligible
	Reproduction: prothioconazole	NOEC: 583.3 mg a.i./kg diet (100 mg a.i./kg bw/day)	147.4 mg a.i./kg dw diet	0.25	Low
	Reproduction: prothioconazole-desthio	NOEC: 160 mg/kg diet	147.4 mg/kg dw diet	0.92	Low

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Risk
	Chronic; developmental; gavage: prothioconazole	NOEL (maternal): 583.3 mg a.i./kg diet	147.4 mg a.i./kg dw diet	0.25	Low
	Chronic; developmental; neurotoxicity; dietary exposure: prothioconazole-desthio	NOEC (maternal, developmental): 40 mg/kg diet	147.4 mg/kg dw diet	3.69	Moderate
Mouse	Acute: prothioconazole-desthio	LD_{50}: 2235 mg/kg bw (males) NOEL: 500 mg/kg bw (mortality)	146.5 mg/kg dw diet	83.9 days 18.8 days	Negligible
Rabbit	Chronic; developmental; gavage: prothioconazole-desthio	NOEL (maternal and developmental): 66.67 mg/kg diet	220.4 mg/kg dw diet	3.31	Moderate
Vascular Plants					
Vascular plant	Seedling emergence: prothioconazole	EC_{25}: ≥ 305 g a.i./ha (shoot height and dry weight); 305 g a.i./ha used	595.5 g a.i./ha	1.95	Moderate
	Vegetative vigour: prothioconazole	EC_{25}: > 305 g a.i./ha; 305 g a.i./ha used due to lack of data	595.5 g a.i./ha	1.95	Moderate

Table 20 Screening Level Acute and Chronic Risk Quotients for Aquatic Organism Exposed to Total Toxic Residues (prothioconazole + prothioconazole-desthio + prothioconazole-*S*-methyl)

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Threshold of Effects
Freshwater Species					
Daphnia magna	Acute: prothioconazole	48-hour NOEC: 0.93 mg a.i./L	0.186 mg/L	0.2	Not exceeded
	Acute: prothioconazole-desthio	48-hour NOEC: 5.5 mg/L	0.186 mg/L	0.03	Not exceeded
	Acute: prothioconazole-*S*-methyl	48-hour NOEC: 0.7 mg/L	0.186 mg/L	0.26	Not exceeded
	Acute: JAU6476 480 SC (EP)	48-hour NOEC: 0.81 mg/L	0.186 mg/L	0.23	Not exceeded
	Chronic: prothioconazole	21-day NOEC (growth and reproduction): 0.51 mg a.i./L	0.186 mg/L	0.36	Not exceeded
	Chronic: prothioconazole-desthio	21-day NOEC (growth): 0.103 mg/L	0.186 mg/L	1.8	Exceeded
Midge (*Chironomus riparius*)	Chronic: prothioconazole-desthio	28-day NOEC (reproduction): between 0.23 and 2.37 mg/L	0.186 mg/L	between 0.08 and 0.81	Not exceeded
Rainbow trout (*Oncorhynchus mykiss*)	Acute: prothioconazole	96-hour NOEC: 0.99 mg a.i./L	0.186 mg/L	0.19	Not exceeded
	Acute: prothioconazole-desthio	96-hour NOEC: 2.22 mg/L (sublethal effects)	0.186 mg/L	0.08	Not exceeded
	Acute: prothioconazole-*S*-methyl	96-hour NOEC: 0.265 mg/L (sublethal effects)	0.186 mg/L	0.7	Not exceeded
	Acute: JAU6476 480 SC (EP)	96-hour NOEC: 1.29 mg a.i./L	0.186 mg/L	0.14	Not exceeded

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Threshold of Effects
Bluegill sunfish (*Lepomis macrochirus*)	Acute: prothioconazole	96-hour NOEC: 1.69 mg a.i./L	0.186 mg/L	0.11	Not exceeded
	Acute: JAU6476 480 SC (EP)	96-hour NOEC: 2.81 mg a.i./L	0.186 mg/L	0.07	Not exceeded
Common carp (*Cyprinus carpio*)	Acute: prothioconazole	96-hour NOEC: 0.91 mg a.i./L (sublethal effects)	0.186 mg/L	0.2	Not exceeded
Fathead minnow (*Pimephales promelas*)	Acute: prothioconazole-desthio	96-hour NOEC: 3.85 mg/L (sublethal effects)	0.186 mg/L	0.05	Not exceeded
	Chronic: prothioconazole-desthio	Life-cycle NOEC: 0.148 mg/L	0.186 mg/L	1.2	Exceeded
Freshwater alga: Green (*Selenastrum capricornutum* or *Scenedesmus subspicatus*)	Acute: prothioconazole	96-hour NOEC: 0.371 mg a.i./L	0.186 mg/L	0.5	Not exceeded
	Acute: prothioconazole-desthio	96-hour NOEC: 0.05 mg/L	0.186 mg/L	3.7	Exceeded
	Acute: prothioconazole-*S*-methyl	96-hour NOEC: < 1.03 mg/L $1/10^{th}$ of the 96-hour EC_{50} (cell density): 0.28 mg/L	0.186 mg/L	0.66	Not exceeded
	Acute: JAU6476 480 SC (EP)	96-hour NOEC: 0.48 mg a.i./L	0.186 mg/L	0.39	Not exceeded
Freshwater alga: Blue-green (*Anabaena flos-aquae*)	Acute: prothioconazole	96-hour NOEC (cell density): 0.82 mg a.i./L	0.186 mg/L	0.23	Not exceeded
Freshwater alga: Diatom (*Navicula pellicu losa*)	Acute: prothioconazole	96-hour NOEC: < 0.0124 mg a.i./L (cell density and biomass) $1/10^{th}$ of the 96-hour EC_{50} (biomass): 0.01217 mg a.i./L	0.186 mg/L	15.3	Exceeded

Organism	Exposure: Test Substance	Endpoint Value	EEC for Total Toxic Residues	RQ	Threshold of Effects
Vascular plant Duckweed (*Lemna gibba*)	Dissolved: prothioconazole	7-day NOEC (frond number and biomass): 0.00334 mg a.i./L	0.186 mg/L	55.7	Exceeded
	Dissolved: prothioconazole-desthio	7-day NOEC: 0.0058 mg/L	0.186 mg/L	32.1	Exceeded
	Dissolved: JAU6476 480 SC (EP)	7-day NOEC: 0.0075 mg a.i./L	0.186 mg/L	24.8	Exceeded
Marine Species					
Crustacean Saltwater mysid (*Mysidopsis bahia*)	Acute: prothioconazole	96-hour NOEC: 0.99 mg a.i./L	0.186 mg/L	0.19	Not exceeded
	Acute: prothioconazole-desthio	96-hour NOEC: 0.026 mg/L	0.186 mg/L	7.2	Exceeded
	Chronic: prothioconazole-desthio	NOEC (reproductive success): 0.064 mg/L	0.186 mg/L	2.9	Exceeded
Mollusk Eastern oyster (*Crassostrea virginica*)	Acute: prothioconazole	96-hour NOEC (reduced shell deposition): 0.76 mg a.i./L	0.186 mg/L	0.24	Not exceeded
Sheepshead minnow (*Cyprinodon variegatus*)	Acute: prothioconazole	96-hour NOEC: 10.3 mg a.i./L	0.186 mg/L	0.018	Not exceeded
Marine alga: Diatom (*Skeletonema costatum*)	Acute: prothioconazole	96-hour NOEC (cell density and biomass): 0.00448 mg a.i./L	0.186 mg/L	41.5	Exceeded

Table 21 Risk Quotients for Aquatic Organisms Determined for Runoff of Total Toxic Residues

Organism	Region	NOEC (mg/L)	EEC 90th percentile of concentrations (mg/L)	RQ	Risk
Freshwater Organisms					
Daphnia magna	British Columbia	0.103	21-day: 0.008	0.08	Negligible
	Prairies	0.103	21-day: 0.0167	0.16	Low
	Ontario	0.103	21-day: 0.0121	0.12	Low
	Quebec	0.103	21-day: 0.011	0.11	Low
	Atlantic	0.103	21-day: 0.0125	0.12	Low
Fathead minnow (*Pimephales promelas*)	British Columbia	0.148	Yearly average: 0.0053	0.04	Negligible
	Prairies	0.148	Yearly average: 0.0091	0.06	Negligible
	Ontario	0.148	Yearly average: 0.0092	0.06	Negligible
	Quebec	0.148	Yearly average: 0.0089	0.06	Negligible
	Atlantic	0.148	Yearly average: 0.0084	0.06	Negligible
Diatom (*Navicula pelliculosa*)	British Columbia	0.01217	96-hour: 0.0097	0.8	Low
	Prairies	0.01217	96-hour: 0.0197	1.6	Moderate
	Ontario	0.01217	96-hour: 0.0139	1.1	Moderate
	Quebec	0.01217	96-hour: 0.0118	0.97	Low
	Atlantic	0.01217	96-hour: 0.0147	1.2	Moderate
Green alga (*Scenedesmus subspicatus*)	British Columbia	0.05	96-hour: 0.0097	0.2	Low
	Prairies	0.05	96-hour: 0.0197	0.4	Low
	Ontario	0.05	96-hour: 0.0139	0.3	Low
	Quebec	0.05	96-hour: 0.0118	0.2	Low
	Atlantic	0.05	96-hour: 0.0147	0.3	Low
Aquatic vascular plant *Lemna gibba* study with prothioconazole	British Columbia	0.00334	96-hour: 0.0097	2.9	Moderate
	Prairies	0.00334	96-hour: 0.0197	5.9	Moderate
	Ontario	0.00334	96-hour: 0.0139	4.2	Moderate
	Quebec	0.00334	96-hour: 0.0118	3.5	Moderate
	Atlantic	0.00334	96-hour: 0.0147	4.4	Moderate

Organism	Region	NOEC (mg/L)	EEC 90th percentile of concentrations (mg/L)	RQ	Risk
Aquatic vascular plant *Lemna gibba* study with prothioconazole -desthio	British Columbia	0.0058	96-hour: 0.0097	1.7	Moderate
	Prairies	0.0058	96-hour: 0.0197	3.4	Moderate
	Ontario	0.0058	96-hour: 0.0139	2.4	Moderate
	Quebec	0.0058	96-hour: 0.0118	2	Moderate
	Atlantic	0.0058	96-hour: 0.0147	2.5	Moderate
Aquatic vascular plant *Lemna gibba* study with JAU6476 480 SC	British Columbia	0.0075	96-hour: 0.0097	1.3	Moderate
	Prairies	0.0075	96-hour: 0.0197	2.6	Moderate
	Ontario	0.0075	96-hour: 0.0139	1.8	Moderate
	Quebec	0.0075	96-hour: 0.0118	1.6	Moderate
	Atlantic	0.0075	96-hour: 0.0147	2	Moderate
Marine Organisms					
Mysid shrimp (*Mysidopsis bahia*) Acute	British Columbia	0.026	96-hour: 0.0097	0.4	Low
	Prairies	0.026	96-hour: 0.0197	N/A	N/A
	Ontario	0.026	96-hour: 0.0139	0.5	Low
	Quebec	0.026	96-hour: 0.0118	0.4	Low
	Atlantic	0.026	96-hour: 0.0147	0.6	Low
Mysid shrimp (*Mysidopsis bahia*) Chronic	British Columbia	0.064	21-day: 0.008	0.12	Low
	Prairies	0.064	21-day: 0.0167	N/A	N/A
	Ontario	0.064	21-day: 0.0121	0.2	Low
	Quebec	0.064	21-day: 0.011	0.2	Low
	Atlantic	0.064	21-day: 0.0125	0.2	Low
Marine diatom (*Skeletonema costatum*)	British Columbia	0.00448	96-hour: 0.0097	2.2	Moderate
	Prairies	0.00448	96-hour: 0.0197	N/A	N/A
	Ontario	0.00448	96-hour: 0.0139	3.1	Moderate
	Quebec	0.00448	96-hour: 0.0118	2.6	Moderate
	Atlantic	0.00448	96-hour: 0.0147	3.3	Moderate

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